WEST Search History

DATE: Monday, June 30, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L5	L4 and atomic coordinates	9	L5
L4	L3 and inhibitor	118	L4
L3	L1 and p38	120	L3
L2	protein kinase same binding site same (three adj2 structure or crystal structure or x-ray structure or nmr structure)	17	L2
L1	protein kinase and binding site and (three adj2 structure or crystal structure or x-ray structure or nmr structure)	2850	L1

END OF SEARCH HISTORY

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 9 of 9 returned.

☐ 1. Document ID: US 20030109021 A1

L5: Entry 1 of 9 File: PGPB Jun 12, 2003

PGPUB-DOCUMENT-NUMBER: 20030109021
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030109021 A1

TITLE: Polynucleotide encoding a novel metalloprotease highly expressed in the testis, MMP-29

PUBLICATION-DATE: June 12, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wu, Shujian	Langhorne	PA	US	
Chen, Jian	Princeton	NJ	US	
Feder, John N.	Belle Mead	NJ	US	
Lee, Liana	North Brunswick	NJ	US	
Krystek, Stanley R.	Ringoes	NJ	US	

US-CL-CURRENT: 435/226; 435/320.1, 435/325, 435/69.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20030096303 A1

L5: Entry 2 of 9 File: PGPB May 22, 2003

PGPUB-DOCUMENT-NUMBER: 20030096303
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030096303 A1

TITLE: Crystallized P38 complexes

PUBLICATION-DATE: May 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Bellon, Steven	Wellesly	MA	US	
Bemis, Guy	Arlington	MA	US	
Wilson, Keith	Boston	MA	US	
Fitzgibbon, Matthew	Millis	MA	US	

US-CL-CURRENT: 435/7.1; 435/194, 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC
Draw Desc | Image

☐ 3. Document ID: US 20030068831 A1

L5: Entry 3 of 9 File: PGPB Apr 10, 2003

PGPUB-DOCUMENT-NUMBER: 20030068831
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030068831 A1

TITLE: Proteins and druggable regions of proteins

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Edwards, Aled	Toronto	CA	CA	
Arrowsmith, Cheryl	North York		CA	
Greenblatt, Jack	Toronto		CA	
Mendlein, John D.	Encincitas		US	

US-CL-CURRENT: 436/518; 435/7.1, 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC
Draw Desc | Image

☐ 4. Document ID: US 20030068651 A1

L5: Entry 4 of 9 File: PGPB Apr 10, 2003

PGPUB-DOCUMENT-NUMBER: 20030068651
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030068651 A1

TITLE: Multi-target analysis of gene families for chemistry of high affinity and selective small molecules and other therapeutics

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Arrowsmith, Cheryl	North York	CA	CA	
Greenblatt, Jack	Toronto		CA	
Edwards, Aled	Toronto		CA	
Mendlein, John D.	Encincitas		US	

US-CL-CURRENT: 435/7.1; 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 5. Document ID: US 20030068650 A1

L5: Entry 5 of 9 File: PGPB Apr 10, 2003

PGPUB-DOCUMENT-NUMBER: 20030068650
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030068650 A1

TITLE: Target analysis for chemistry of specific and broad spectrum anti-infectives and other therapeutics

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Greenblatt, Jack	Toronto	CA	CA	
Edwards, Aled	Toronto		CA	
Arrowsmith, Cheryl	North York		CA	
Mendlein, John D.	Encincitas		US	

US-CL-CURRENT: 435/7.1; 435/5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 6. Document ID: US 20030055219 A1

L5: Entry 6 of 9 File: PGPB Mar 20, 2003

PGPUB-DOCUMENT-NUMBER: 20030055219
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030055219 A1

TITLE: Protein-protein interactions

PUBLICATION-DATE: March 20, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cimbora, Daniel M.	Salt Lake City	UT	US	
Heichman, Karen	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 530/350; 435/7.1, 530/388.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 7. Document ID: US 20030032058 A1

L5: Entry 7 of 9 File: PGPB Feb 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030032058
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030032058 A1

TITLE: Protein-protein interactions

PUBLICATION-DATE: February 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cimbora, Daniel M.	Salt Lake City	UT	US	
Heichman, Karen	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 435/7.1; 435/7.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 8. Document ID: US 20020164615 A1

L5: Entry 8 of 9 File: PGPB Nov 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020164615
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020164615 A1

TITLE: Protein-protein interactions

PUBLICATION-DATE: November 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cimbora, Daniel M.	Salt Lake City	UT	US	
Heichman, Karen	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 435/6; 435/183, 435/7.2, 530/388.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 9. Document ID: US 6387641 B1

L5: Entry 9 of 9 File: USPT May 14, 2002

US-PAT-NO: 6387641
DOCUMENT-IDENTIFIER: US 6387641 B1

TITLE: Crystallized P38 complexes

DATE-ISSUED: May 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bellon; Steven	Wellesly	MA		
Bemis; Guy	Arlington	MA		
Wilson; Keith	Boston	MA		
Fitzgibbon; Matthew	Millis	MA		

US-CL-CURRENT: 435/15; 702/19, 702/22

ABSTRACT:

This invention provides certain crystallized, protein kinase-ligand complexes, in particular P38-ligand complexes, and their structure coordinates. The structure coordinates are based on the structure of a phosphorylated P38.gamma. complex which has now been solved and which reveals new structural information useful for understanding the activated states of other, related kinase proteins as described herein. The key structural features of the proteins, particularly the shape of the substrate binding site, are useful in methods for designing or identifying selective inhibitors of the protein kinases, particularly P38.gamma. and in solving the structures of other proteins with similar features. The structure coordinates may be encoded in a data storage medium for use with a computer for graphical three-dimensional representation of the structure and for computer-aided molecular design of new inhibitors.

17 Claims, 147 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 146

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 17 of 17 returned.

☐ 1. Document ID: US 20030118988 A1

L2: Entry 1 of 17 File: PGPB Jun 26, 2003

PGPUB-DOCUMENT-NUMBER: 20030118988
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030118988 A1

TITLE: BRAIN AND HEART CYCLIC NUCLEOTIDE GATED ION CHANNEL COMPOUNDS AND USES THEREOF

PUBLICATION-DATE: June 26, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
KANDEL, ERIC R.	RIVERDALE	NY	US	
SANTORO, BINA	ROMA	NY	IT	
BARTSCH, DUSAN	NEW YORK	NY	US	
SIEGELBAUM, STEVEN	NEW YORK	NY	US	
TIBBS, GARETH	NEW YORK		US	
GRANT, SETH	EDINBURGH		GB	

US-CL-CURRENT: 435/6; 435/320.1, 435/325, 435/69.1, 530/350, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20030073218 A1

L2: Entry 2 of 17 File: PGPB Apr 17, 2003

PGPUB-DOCUMENT-NUMBER: 20030073218
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030073218 A1

TITLE: High affinity inhibitors for target validation and uses thereof

PUBLICATION-DATE: April 17, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Shokat, Kevan M.	San Francisco	CA	US	

US-CL-CURRENT: 435/184; 424/94.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 3. Document ID: US 20030032649 A1

L2: Entry 3 of 17 File: PGPB Feb 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030032649
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030032649 A1

TITLE: Chimerizing protein kinases for drug discovery

PUBLICATION-DATE: February 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Goldsmith, Elizabeth J.	Dallas	TX	US	
Radha, Akella	Plano	TX	US	
Gaynor, Richard B.	Dallas	TX	US	

US-CL-CURRENT: 514/263.1; 435/194, 514/46, 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 4. Document ID: US 20020155503 A1

L2: Entry 4 of 17 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020155503
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020155503 A1

TITLE: Method for mapping the active sites bound by enzymes that covalently modify substrate molecules

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Clark, Jonathan	Cambridge		GB	
Lamont, Alan	Herts		GB	
Williams, David	Herts		GB	

US-CL-CURRENT: 435/7.1; 436/518

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 5. Document ID: US 20020146797 A1

L2: Entry 5 of 17 File: PGPB Oct 10, 2002

PGPUB-DOCUMENT-NUMBER: 20020146797
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020146797 A1

TITLE: Engineered protein kinases which can utilize modified nucleotide triphosphate substrates

PUBLICATION-DATE: October 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Shokat, Kevan M.	San Francisco	CA	US	

US-CL-CURRENT: 435/194; 435/320.1, 435/325, 435/69.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 6. Document ID: US 20020016976 A1

L2: Entry 6 of 17 File: PGPB Feb 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020016976
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020016976 A1

TITLE: Engineered protein kinases which can utilize modified nucleotide triphosphate substrates

PUBLICATION-DATE: February 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Shokat, Kevan M.	San Francisco	CA	US	

US-CL-CURRENT: 800/8; 424/94.5, 435/15, 435/194, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 7. Document ID: US 6551821 B1

L2: Entry 7 of 17 File: USPT Apr 22, 2003

US-PAT-NO: 6551821
DOCUMENT-IDENTIFIER: US 6551821 B1

TITLE: Brain cyclic nucleotide gated ion channel and uses thereof

DATE-ISSUED: April 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kandel; Eric R.	Riverdale	NY		
Santoro; Bina	Roma			IT
Bartsch; Dusan	New York	NY		
Siegelbaum; Steven	New York	NY		
Tibbs; Gareth	New York	NY		
Grant; Seth	Edinburgh			GB

US-CL-CURRENT: 435/325; 435/252.33, 435/320.1, 514/44, 536/23.1, 536/23.5

ABSTRACT:

The present invention provides an isolated nucleic acid molecule encoding a brain cyclic nucleotide gated ion channel (BCNG) protein. An isolated BCNG protein is also provided as is a composition comprising a BCNG encoding nucleic acid or protein or a portion thereof. The present invention also provides a method of identifying an ion channel subunit related protein encoding nucleic acid molecule in a sample. The invention further provides a method for evaluating the ability of a compound to modulate an ion channel associated neurological, cardia, or renal condition. The invention also provides a method for evaluating the ability of a compound to interact with a BCNG-related ion channel subunit protein. Additionally, the present invention provides a method for identifying a compound capable of modulating the activity of a BCNG-related protein. The present invention additionally provides a method of treating a cardiac, renal or neurological condition. Finally, the present invention provides an antibody which specifically reacts with BCNG protein.

10 Claims, 37 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 22

8. Document ID: US 6521417 B1

L2: Entry 8 of 17 File: USPT Feb 18, 2003

US-PAT-NO: 6521417
DOCUMENT-IDENTIFIER: US 6521417 B1

TITLE: Engineered protein kinases which can utilize modified nucleotide triphosphate substrates

DATE-ISSUED: February 18, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shokat; Kevan M.	San Francisco	CA		

US-CL-CURRENT: 435/15; 435/194

ABSTRACT:

Engineered protein kinases which can utilize modified nucleotide triphosphate substrates that are not as readily utilized by the wild-type forms of those enzymes, and methods of making and using them are disclosed. Modified nucleotide triphosphate substrates and methods of making and using them are disclosed. Methods are disclosed for using such engineered kinases and such modified substrates to identify which protein substrates the kinases act upon, to measure the extent of such action, and to determine if test compounds can modulate such action. Engineered forms of multi-substrate enzymes which covalently attach part or all of at least one (donor) substrate to at least one other (recipient) substrate, which engineered forms will accept modified substrates that are not as readily utilized by the wild-type forms of those enzymes are disclosed. Methods for making and using such engineered enzymes are disclosed. Modified substrates and methods of making and using them are disclosed. Methods are disclosed for using such engineered enzymes and such modified substrates to identify the recipient substrates the enzymes act upon, to measure the extent of such action, and to measure whether test compounds modulate such action.

8 Claims, 44 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 24

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 9. Document ID: US 6390821 B1

L2: Entry 9 of 17 File: USPT May 21, 2002

US-PAT-NO: 6390821
DOCUMENT-IDENTIFIER: US 6390821 B1

TITLE: Engineered protein kinases which can utilize modified nucleotide triphosphate substrates

DATE-ISSUED: May 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shokat; Kevan M.	San Francisco	CA		

US-CL-CURRENT: 434/194; 536/23.2

ABSTRACT:

Engineered protein kinases which can utilize modified nucleotide triphosphate substrates that are not as readily utilized by the wild-type forms of those enzymes, and methods of making and using them. Modified nucleotide triphosphate substrates and methods of making and using them. Methods for using such engineered kinases and such modified substrates to identify which protein substrates the kinases act upon, to measure the extent of such action, and to determine if test compounds can modulate such action. Also engineered forms of multi-substrate enzymes which covalently attach part or all of at least one (donor) substrate to at least one other (recipient) substrate, which engineered forms will accept modified substrates that are not as readily utilized by the wild-type forms of those enzymes. Methods for making and using such engineered enzymes. Modified substrates and methods of making and using them. Methods for using such engineered enzymes and such modified substrates to identify the recipient substrates the enzymes act upon, to measure the extent of such action, and to measure whether test compounds modulate such action.

6 Claims, 41 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 24

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 10. Document ID: US 6383790 B1

L2: Entry 10 of 17 File: USPT May 7, 2002

US-PAT-NO: 6383790
DOCUMENT-IDENTIFIER: US 6383790 B1

TITLE: High affinity protein kinase inhibitors

DATE-ISSUED: May 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shokat; Kevan M.	San Francisco	CA		

US-CL-CURRENT: 435/194; 435/184, 514/262.1, 544/262

ABSTRACT:

This invention provides general methods for discovering mutant inhibitors for any class of enzymes as well as the specific inhibitors so identified. More specifically, this invention provides general methods for discovering specific inhibitors for multi-substrate enzymes. Examples of such multi-substrate enzymes include, but are not limited to, kinases and transferases. The mutant inhibitors identified by the methods of this invention can be used to highly selectively disrupt cell functions such as oncogenic transformation. In one particular example, this invention provides a Src protein kinase inhibitor, pharmaceutical compositions thereof and methods of disrupting transformation in a cell that expresses the target v-scr comprising contacting the cell with the protein kinase inhibitor.

60 Claims, 65 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 37

☐ 11. Document ID: US 6377893 B1

L2: Entry 11 of 17 File: USPT Apr 23, 2002

US-PAT-NO: 6377893
DOCUMENT-IDENTIFIER: US 6377893 B1

TITLE: Application of protein structure predictions

DATE-ISSUED: April 23, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Benner; Steven Albert	Gainesvillle	FL	32605	

US-CL-CURRENT: 702/20; 436/86, 436/89, 702/27, 702/31

ABSTRACT:

A method for making a model for the folded structure of a set of proteins from an evolutionary analysis of a set of aligned homologous protein sequences was claimed in Ser. No. 07/857,224. The instant application concerns methods for using these models. The first method is used to confirm or deny a hypothesis that two proteins are homologous, and is comprised of comparing a predicted structure model for one family of proteins with a predicted structure model for a second family of proteins, or an experimental structure for the second family, and deducing the presence or absence of homology based on the presence or absence of structural similarity flanking key residue motifs in the polypeptide sequence. The second method identifies mutations during the divergent evolution of a protein sequence that are potentially adaptive by identifying episodes during the divergent evolution of a family of proteins where there is a high absolute rate of amino acid substitution, or a high ratio of non-silent substitutions to non-silent substitutions. Amino acids that are changing during this episode are likely to be adaptive. The third is a method for identifying specific in vitro properties of the protein that are likely to play a physiological role in vivo in an organism. This methods involves synthesizing in the laboratory proteins having the reconstructed amino acid sequences of a protein before and after a period of rapid sequence evolution that characterizes adaptive substitution, measuring the in vitro

properties of the protein before the episode of rapid sequence evolution, and then measuring the in vivo properties of the protein after the episode of rapid sequence evolution. The in vitro behaviors that remained unchanged through this episode are not likely to have adaptive significance physiologically. The in vitro behaviors that changed through this episode are likely to have adaptive significance physiologically. The fourth concerns method for organizing genome sized sequence databases.

23 Claims, 2 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 12. Document ID: US 6365626 B1

L2: Entry 12 of 17 File: USPT Apr 2, 2002

US-PAT-NO: 6365626
DOCUMENT-IDENTIFIER: US 6365626 B1

TITLE: BTK inhibitors and methods for their identification and use

DATE-ISSUED: April 2, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Zheng; Yaguo	New Brighton	MN		
Ghosh; Sutapa	Shoreview	MN		

US-CL-CURRENT: 514/521; 514/238.5, 514/331, 514/423, 514/548, 544/163, 546/230, 548/567, 558/392, 560/250

ABSTRACT:

The invention provides BTK inhibitors, methods for their identification and use, and pharmaceutical compositions comprising BTK inhibitors.

3 Claims, 73 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 39

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 13. Document ID: US 6303652 B1

L2: Entry 13 of 17 File: USPT Oct 16, 2001

US-PAT-NO: 6303652
DOCUMENT-IDENTIFIER: US 6303652 B1
**** See image for Certificate of Correction ****

TITLE: BTK inhibitors and methods for their identification and use

DATE-ISSUED: October 16, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Zheng; Yaguo	New Brighton	MN		
Ghosh; Sutapa	Shoreview	MN		

US-CL-CURRENT: 514/521; 514/227.5, 514/238.5, 514/331, 514/428, 514/548, 544/163, 544/58.4, 546/230, 548/567, 558/392, 560/250

ABSTRACT:

The invention provides BTK inhibitors, methods for their identification and use, and pharmaceutical compositions comprising BTK inhibitors.

4 Claims, 73 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 39

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 14. Document ID: US 6294575 B1

L2: Entry 14 of 17 File: USPT Sep 25, 2001

US-PAT-NO: 6294575
DOCUMENT-IDENTIFIER: US 6294575 B1

TITLE: BTK inhibitors and methods for their identification and use

DATE-ISSUED: September 25, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Zheng; Yaguo	New Brighton	MN		
Ghosh; Sutapa	Shoreview	MN		

US-CL-CURRENT: 514/521; 514/238.5, 514/331, 514/428, 514/548, 544/163, 546/230, 548/567, 558/392, 560/250

ABSTRACT:

The invention provides BTK inhibitors, methods for their identification and use, and pharmaceutical compositions comprising BTK inhibitors.

6 Claims, 73 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 39

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 15. Document ID: US 6221900 B1

L2: Entry 15 of 17 File: USPT Apr 24, 2001

US-PAT-NO: 6221900
DOCUMENT-IDENTIFIER: US 6221900 B1
**** See image for Certificate of Correction ****

TITLE: BTK inhibitors and methods for their identification and use

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Zheng; Yaguo	New Brighton	MN		
Ghosh; Sutapa	Shoreview	MN		

US-CL-CURRENT: 514/457; 514/312, 514/432, 546/156, 546/157, 549/23, 549/399, 549/404, 549/405, 549/407

ABSTRACT:

The invention provides BTK inhibitors, methods for their identification and use, and pharmaceutical compositions comprising BTK inhibitors.

15 Claims, 73 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 39

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 16. Document ID: US 6160010 A

L2: Entry 16 of 17 File: USPT Dec 12, 2000

US-PAT-NO: 6160010
DOCUMENT-IDENTIFIER: US 6160010 A

TITLE: BTK inhibitors and methods for their identification and use

DATE-ISSUED: December 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Zheng; Yaguo	New Brighton	MN		
Ghosh; Sutapa	Shoreview	MN		

US-CL-CURRENT: 514/521; 514/238.5, 514/331, 514/428, 514/548, 544/163, 546/230, 548/567, 558/392, 560/250

ABSTRACT:

The invention provides BTK inhibitors, methods for their identification and use, and pharmaceutical compositions comprising BTK inhibitors.

6 Claims, 28 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 39

☐ 17. Document ID: EP 1096014 A2

L2: Entry 17 of 17 File: EPAB May 2, 2001

PUB-NO: EP001096014A2
DOCUMENT-IDENTIFIER: EP 1096014 A2
TITLE: Catalytic domain of the human effector cell cycle checkpoint protein kinase, Chk1, materials and methods for identification of inhibitors thereof

PUBN-DATE: May 2, 2001

INVENTOR-INFORMATION:

NAME	COUNTRY
CHEN, PING	US
KAN, CHEN-CHEN	US
LUO, CHUN	US
MARGOSIAK, STEPHEN	US
O'CONNOR, PATRICK	US
TEMPCZYK-RUSSEL, ANNA	US
NGUYEN, BINH	US
SARUP, JAY CHAND	US
GAUR, SMITA	US
ANDERSON, MARK BRIAN	US
DENG, YA-LI	US
LUNDGREN, KAREN	US
REGISTER, JAMES	US

INT-CL (IPC): C12 N 15/54; C12 N 9/12; C12 Q 1/34
EUR-CL (EPC): C12N009/12; C12Q001/34

ABSTRACT:

CHG DATE=20010601 STATUS=O> The present invention relates to the identification, isolation and purification of the catalytic domain of the human effector checkpoint protein kinase (hChk1). A 1.7 &cir& crystal structure of the hChk1 kinase domain in the active conformation is reported herein. The kinase domain of hChk1 and its associated crystal structure is described for use in the discovery, identification and characterization of inhibitors of hChk1. This structure provides a three-dimensional description of the binding site of the hChk1 for structure-based design of small molecule inhibitors thereof as therapeutic agents. Inhibitors of hChk1 find utility in the treatment of hyperproliferative disorders such as HIV and cancer.

Generate Collection Print

```
=> file .nash
=> s protein kinase and binding site
L1        6557 FILE MEDLINE
L2        3401 FILE CAPLUS
L3        4157 FILE SCISEARCH
L4        1098 FILE LIFESCI
L5        2928 FILE BIOSIS
L6        3636 FILE EMBASE

TOTAL FOR ALL FILES
L7       21777 PROTEIN KINASE AND BINDING SITE

=> s l7 and (three (5w) dimentional or x-ray structure)

TOTAL FOR ALL FILES
L14         65 L7 AND (THREE (5W) DIMENTIONAL OR X-RAY STRUCTURE)

=> s l7 and nmr (5w) structure

TOTAL FOR ALL FILES
L21         67 L7 AND NMR (5W) STRUCTURE

=> s l14 or l21
TOTAL FOR ALL FILES
L28        123 L14 OR L21

=> s l28 and p38
TOTAL FOR ALL FILES
L35          1 L28 AND P38

=> d ibib abs

L35  ANSWER 1 OF 1  SCISEARCH  COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER:   1999:490206  SCISEARCH
THE GENUINE ARTICLE: 208AB
TITLE:              Structural analysis of the lymphocyte-specific kinase Lck
                    in complex with non-selective and Src family selective
                    kinase inhibitors
AUTHOR:             Zhu X T (Reprint); Kim J L; Newcomb J R; Rose P E; Stover
                    D R; Toledo L M; Zhao H L; Morgenstern K A
CORPORATE SOURCE:   KINETIX PHARMACEUT INC, MEDFORD, MA 02155 (Reprint)
COUNTRY OF AUTHOR:  USA
SOURCE:             STRUCTURE WITH FOLDING & DESIGN, (15 JUN 1999) Vol. 7, No.
                    6, pp. 651-661.
                    Publisher: CURRENT BIOLOGY LTD, 34-42 CLEVELAND STREET,
                    LONDON W1P 6LE, ENGLAND.
                    ISSN: 0969-2126.
DOCUMENT TYPE:      Article; Journal
FILE SEGMENT:       LIFE
LANGUAGE:           English
REFERENCE COUNT:    63
                   *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
```

AB Background: The lymphocyte-specific kinase Lck is a member of the Src family of non-receptor tyrosine kinases. Lck catalyzes the initial phosphorylation of T-cell receptor components that is necessary for signal transduction and T-cell activation. On the basis of both biochemical and genetic studies, Lck is considered an attractive cell-specific target for the design of novel T-cell immunosuppressants. To date, the lack of detailed structural information on the mode of inhibitor binding to Lck has limited the discovery of novel Lck inhibitors.

Results: We report here the high-resolution crystal structures of an activated Lck kinase domain in complex with three structurally distinct ATP-competitive inhibitors: AMP-PNP (a non-selective, non-hydrolyzable ATP analog); staurosporine (a potent but non-selective **protein kinase** inhibitor); and PP2 (a potent Src family selective protein tyrosine kinase inhibitor). Comparison of these structures reveals subtle but important structural changes at the ATP-**binding site** . Furthermore, PP2 is found to access a deep, hydrophobic pocket near the ATP-binding cleft of the enzyme; this binding pocket is not occupied by either AMP-PNP or staurosporine.

Conclusions: The potency of staurosporine against Lck derives in part from an induced movement of the glycine-rich loop of the enzyme upon binding of this ligand, which maximizes the van der Waals interactions present in the complex. In contrast, PP2 binds tightly and selectively to Lck and other Src family kinases by making additional contacts in a deep, hydrophobic pocket adjacent to the ATP-**binding site**; the amino acid composition of this pocket is unique to Src family kinases. The structures of these Lck complexes offer useful structural insights as they demonstrate that kinase selectivity can be achieved with small-molecule inhibitors that exploit subtle topological differences among **protein kinases**.

=> s l28 not 2002-2003/py
TOTAL FOR ALL FILES
L42 99 L28 NOT 2002-2003/PY

=> dup rem l42
PROCESSING COMPLETED FOR L42
L43 53 DUP REM L42 (46 DUPLICATES REMOVED)

=> d ibib abs 1-53

L43 ANSWER 1 OF 53 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001460685 MEDLINE
DOCUMENT NUMBER: 21376042 PubMed ID: 11483498
TITLE: Structure and ligand recognition of the PB1 domain: a novel protein module binding to the PC motif.
AUTHOR: Terasawa H; Noda Y; Ito T; Hatanaka H; Ichikawa S; Ogura K; Sumimoto H; Inagaki F
CORPORATE SOURCE: Tokyo Metropolitan Institute of Medical Science, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8613, Japan.
SOURCE: EMBO JOURNAL, (2001 Aug 1) 20 (15) 3947-56.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1IPG
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20030215
Entered Medline: 20010927
AB PB1 domains are novel protein modules capable of binding to target proteins that contain PC motifs. We report here the **NMR structure** and ligand-**binding site** of the PB1 domain of the cell polarity establishment protein, Bem1p. In addition, we identify the topology of the PC motif-containing region of Cdc24p by NMR, another cell polarity establishment protein that interacts with Bem1p. The PC motif-containing region is a structural domain offering a scaffold to the PC motif. The chemical shift perturbation experiment and the mutagenesis study show that the PC motif is a major structural element that binds to the PB1 domain. A structural database search reveals close similarity between the Bem1p PB1 domain and the c-Raf1 Ras-binding domain. However, these domains are functionally distinct from each other.

L43 ANSWER 2 OF 53 MEDLINE
ACCESSION NUMBER: 2001460682 MEDLINE
DOCUMENT NUMBER: 21376039 PubMed ID: 11483495
TITLE: **X-ray structure** of HPr kinase: a bacterial **protein kinase** with a P-loop nucleotide-binding domain.
AUTHOR: Fieulaine S; Morera S; Poncet S; Monedero V; Gueguen-Chaignon V; Galinier A; Janin J; Deutscher J; Nessler S
CORPORATE SOURCE: Laboratoire d'Enzymologie et Biochimie Structurales, UPR 9063, CNRS, 91198 Gif sur Yvette, France.
SOURCE: EMBO JOURNAL, (2001 Aug 1) 20 (15) 3917-27.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20020420
Entered Medline: 20010927

AB HPr kinase/phosphatase (HprK/P) is a key regulatory enzyme controlling carbon metabolism in Gram- positive bacteria. It catalyses the ATP-dependent phosphorylation of Ser46 in HPr, a protein of the phosphotransferase system, and also its dephosphorylation. HprK/P is unrelated to eukaryotic **protein kinases**, but contains the Walker motif A characteristic of nucleotide-binding proteins. We report here the **X-ray structure** of an active fragment of Lactobacillus casei HprK/P at 2.8 A resolution, solved by the multiwavelength anomalous dispersion method on a seleniated protein (PDB code 1jb1). The protein is a hexamer, with each subunit containing an ATP-binding domain similar to nucleoside/nucleotide kinases, and a putative HPr-binding domain unrelated to the substrate-binding domains of other kinases. The Walker motif A forms a typical P-loop which binds inorganic phosphate in the crystal. We modelled ATP binding by comparison with adenylate kinase, and designed a tentative model of the complex with HPr based on a docking simulation. The results confirm that HprK/P represents a new family of **protein kinases**, first identified in bacteria, but which may also have members in eukaryotes.

L43 ANSWER 3 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2001:367284 SCISEARCH
THE GENUINE ARTICLE: 424JL
TITLE: Treble clef finger - a functionally diverse zinc-binding structural motif
AUTHOR: Grishin N V (Reprint)
CORPORATE SOURCE: Univ Texas, SW Med Ctr, Howard Hughes Med Inst, 5323 Harry Hines Blvd, Dallas, TX 75390 USA (Reprint); Univ Texas, SW Med Ctr, Howard Hughes Med Inst, Dallas, TX 75390 USA; Univ Texas, SW Med Ctr, Dept Biochem, Dallas, TX 75390 USA
COUNTRY OF AUTHOR: USA
SOURCE: NUCLEIC ACIDS RESEARCH, (15 APR 2001) Vol. 29, No. 8, pp. 1703-1714.
Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
ISSN: 0305-1048.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 81

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Detection of similarity is particularly difficult for small proteins and thus connections between many of them remain unnoticed. Structure and sequence analysis of several metal-binding proteins reveals unexpected similarities in structural domains classified as different protein folds in SCOP and suggests unification of seven folds that belong to two protein classes. The common motif, termed treble clef finger in this study, forms the protein structural core and is 25-45 residues long, The treble clef motif is assembled around the central zinc ion and consists of a zinc knuckle, loop, P-hairpin and an a-helix, The knuckle and the first turn of the helix each incorporate two zinc ligands. Treble clef domains constitute the core of many structures such as ribosomal proteins L24E and S14, RING fingers, **protein kinase** cysteine-rich domains, nuclear receptor-like fingers, LIM domains, phosphatidylinositol-3-phosphate-binding domains and His-Me finger endonucleases, The treble clef finger is a uniquely versatile motif adaptable for various functions. This small domain with a 25 residue structural core can accommodate eight different metal-**binding sites** and can have many types of functions from binding of nucleic acids, proteins and small molecules, to catalysis of phosphodiester bond hydrolysis, Treble clef motifs are frequently incorporated in larger structures or occur in doublets. Present analysis suggests that the treble clef motif defines a distinct structural fold found in proteins with diverse functional properties and forms one of the major zinc finger groups.

L43 ANSWER 4 OF 53 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001294372 MEDLINE

DOCUMENT NUMBER: 21255900 PubMed ID: 11356104
TITLE: Structural basis of binding of high-affinity ligands to **protein kinase** C: prediction of the binding modes through a new molecular dynamics method and evaluation by site-directed mutagenesis.
AUTHOR: Pak Y; Enyedy I J; Varady J; Kung J W; Lorenzo P S; Blumberg P M; Wang S
CORPORATE SOURCE: Lombardi Cancer Center and Departments of Oncology and Neuroscience, The Research Building, Room WP05, Georgetown University Medical Center, Washington, DC 20007, USA.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2001 May 24) 44 (11) 1690-701.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB The structural basis of **protein kinase** C (PKC) binding to several classes of high-affinity ligands has been investigated through complementary computational and experimental methods. Employing a recently developed q-jumping molecular dynamics (MD) simulation method, which allows us to consider the flexibility of both the ligands and the receptor in docking studies, we predicted the binding models of phorbol-13-acetate, phorbol-12,13-dibutyrate (PDBu), indolactam V (ILV), ingenol-3-benzoate, and thymeleatoxin to PKC. The "predicted" binding model for phorbol-13-acetate is virtually identical to the experimentally determined binding model for this ligand. The predicted binding model for PDBU is the same as that for phorbol-13-acetate in terms of the hydrogen-bonding network and hydrophobic contacts. The predicted binding model for ILV is the same as that obtained in a previous docking study using a Monte Carlo method and is consistent with the structure-activity relationships for this class of ligands. Together with the **X-ray structure** of phorbol-13-acetate in complex with PKCdelta C1b, the predicted binding models of PDBu, ILV, ingenol-3-benzoate, and thymeleatoxin in complex with PKC showed that the binding of these ligands to PKC is governed by a combination of several highly specific and optimal hydrogen bonds and hydrophobic contacts. However, the hydrogen-bonding network for each class of ligand is somewhat different and the number of hydrogen bonds formed between PKC and these ligands has no correlation with their binding affinities. To provide a direct and quantitative assessment of the contributions of several conserved residues around the **binding site** to PKC-ligand binding, we have made 11 mutations and measured the binding affinities of the high-affinity PKC ligands to these mutants. The results obtained through site-directed mutagenic analysis support our predicted binding models for these ligands and provide new insights into PKC-ligand binding. Although all the ligands have high affinity for the wild-type PKCdelta C1b, our site-directed mutagenic results showed that ILV is the ligand most sensitive to structural perturbations of the **binding site** while ingenol-3-benzoate is the least sensitive among the four classes of ligands examined here. Finally, we have employed conventional MD simulations to investigate the structural perturbations caused by each mutation to further examine the role played by each individual residue in PKC-ligand binding. MD simulations revealed that several mutations, including Pro11 --> Gly, Leu21 --> Gly, Leu24 --> Gly, and Gln27 --> Gly, cause a rather large conformational alteration to the PKC **binding site** and, in some cases, to the overall structure of the protein. The complete abolishment or the significant reduction in PKC-ligand binding observed for these mutants thus reflects the loss of certain direct contacts between the side chain of the mutated residue in PKC and ligands as well as the large conformational alteration to the **binding site** caused by the mutation.

L43 ANSWER 5 OF 53 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002116066 MEDLINE
DOCUMENT NUMBER: 21836174 PubMed ID: 11846568
TITLE: Solution structure of the yeast Rad53 FHA2 complexed with a

phosphothreonine peptide pTXXL: comparison with the structures of FHA2-pYXL and FHA1-pTXXD complexes.

AUTHOR: Byeon I J; Yongkiettrakul S; Tsai M D

CORPORATE SOURCE: Department of Chemistry, The Ohio State University, Columbus, OH 43210, USA.. Byeon.2@osu.edu

CONTRACT NUMBER: CA87031 (NCI)

SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (2001 Nov 30) 314 (3) 577-88. Journal code: 2985088R. ISSN: 0022-2836.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: PDB-1J4K; PDB-1J4L; PDB-1K2M; PDB-1K2N

ENTRY MONTH: 200202

ENTRY DATE: Entered STN: 20020220
Last Updated on STN: 20020228
Entered Medline: 20020227

AB It was proposed previously that the FHA2 domain of the yeast **protein kinase** Rad53 has dual specificity toward pY and pT peptides. The consensus sequences of pY peptides for binding to FHA2, as well as the solution structures of free FHA2 and FHA2 complex with a pY peptide derived from Rad9, have been obtained previously. We now report the use of a pT library to screen for binding of pT peptides with the FHA2 domain. The results show that FHA2 binds favorably to pT peptides with Ile at the +3 position. We then searched the Rad9 sequences with a pTXXI/L motif, and tested the binding affinity of FHA2 toward ten pT peptides derived from Rad9. One of the peptides, (599)EVEL(pT)QELP(607), displayed the best binding affinity (K(d)=12.9 microM) and the greatest chemical shift changes. The structure of the FHA2 complex with this peptide was then determined by solution **NMR** and the **structure** of the complex between FHA2 and the pY peptide (826)EDI(pY)YLD(832) was further refined. Structural comparison of these two complexes indicates that the Leu residue at the +3 position in the pT peptide and that at the +2 position in the pY peptide occupy a very similar position relative to the **binding site** residues from FHA2. This can explain why FHA2 is able to bind both pT and pY peptides. This position change from +3 to +2 could be the consequence of the size difference between Thr and Tyr. Further insight into the structural basis of ligand specificity of FHA domains was obtained by comparing the structures of the FHA2-pTXXL complex obtained in this work and the FHA1-pTXXD complex reported in the accompanying paper.
Copyright 2001 Academic Press.

L43 ANSWER 6 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI

ACCESSION NUMBER: 2001:933377 SCISEARCH

THE GENUINE ARTICLE: 495MG

TITLE: Zinc coordination sphere in biochemical zinc sites

AUTHOR: Auld D S (Reprint)

CORPORATE SOURCE: Harvard Univ, Sch Med, Ctr Biochem & Biophys Sci & Med, Boston, MA 02115 USA (Reprint); Harvard Univ, Sch Med, Dept Pathol, Boston, MA 02115 USA

COUNTRY OF AUTHOR: USA

SOURCE: BIOMETALS, (SEP 2001) Vol. 14, No. 3-4, pp. 271-313. Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS. ISSN: 0966-0844.

DOCUMENT TYPE: General Review; Journal

LANGUAGE: English

REFERENCE COUNT: 357

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Zinc is known to be indispensable to growth and development and transmission of the genetic message. It does this through a remarkable mosaic of zinc binding motifs that orchestrate all aspects of metabolism. There are now nearly 200 three dimensional structures for zinc proteins, representing all six classes of enzymes and covering a wide range of phyla and species. These structures provide standards of reference for the identity and nature of zinc ligands in other proteins for which only the primary structure is known. Three primary types of zinc sites are apparent from examination of these structures: structural, catalytic and cocatalytic. The most common amino acids that supply ligands to these sites are His, Glu, Asp and Cys. In catalytic sites zinc generally forms

complexes with water and any three nitrogen, oxygen and sulfur donors with His being the predominant amino acid chosen. Water is always a ligand to such sites. Structural zinc sites have four protein ligands and no bound water molecule. Cys is the preferred ligand in such sites. Cocatalytic sites contain two or three metals in close proximity with two of the metals bridged by a side chain moiety of a single amino acid residue, such as Asp, Glu or His and sometimes a water molecule. Asp and His are the preferred amino acids for these sites. No Cys ligands are found in such sites. The scaffolding of the zinc sites is also important to the function and reactivity of the bound metal. The influence of zinc on quaternary protein structure has led to the identification of a fourth type of zinc **binding site**, protein interface. In this case zinc sites are formed from ligands supplied from amino acid residues residing in the binding surface of two proteins. The resulting zinc site usually has the coordination properties of a catalytic or structural zinc **binding site**.

L43 ANSWER 7 OF 53 MEDLINE
ACCESSION NUMBER: 2000283655 MEDLINE
DOCUMENT NUMBER: 20283655 PubMed ID: 10748115
TITLE: Substrate recognition by the Lyn protein-tyrosine kinase. **NMR structure** of the immunoreceptor tyrosine-based activation motif signaling region of the B cell antigen receptor.
AUTHOR: Gaul B S; Harrison M L; Geahlen R L; Burton R A; Post C B
CORPORATE SOURCE: Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, Indiana 47907-1333, USA.
CONTRACT NUMBER: K04GM00661 (NIGMS)
R01CA37372 (NCI)
R01GM39478 (NIGMS)
+
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 May 26) 275 (21) 16174-82.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000630

AB The immunoreceptor tyrosine-based activation motif (ITAM) plays a central role in transmembrane signal transduction in hematopoietic cells by mediating responses leading to proliferation and differentiation. An initial signaling event following activation of the B cell antigen receptor is phosphorylation of the CD79a (Ig-alpha) ITAM by Lyn, a Src family protein-tyrosine kinase. To elucidate the structural basis for recognition between the ITAM substrate and activated Lyn kinase, the structure of an ITAM-derived peptide bound to Lyn was determined using exchange-transferred nuclear Overhauser NMR spectroscopy. The bound substrate structure has an irregular helix-like character. Docking based on the NMR data into the active site of the closely related Lck kinase strongly favors ITAM binding in an orientation similar to binding of cyclic AMP-dependent **protein kinase** rather than that of insulin receptor tyrosine kinase. The model of the complex provides a rationale for conserved ITAM residues, substrate specificity, and suggests that substrate binds only the active conformation of the Src family tyrosine kinase, unlike the ATP cofactor, which can bind the inactive form.

L43 ANSWER 8 OF 53 MEDLINE
ACCESSION NUMBER: 2002052522 MEDLINE
DOCUMENT NUMBER: 21638650 PubMed ID: 11106755
TITLE: The molecular basis of FHA domain:phosphopeptide binding specificity and implications for phospho-dependent signaling mechanisms.
AUTHOR: Durocher D; Taylor I A; Sarbassova D; Haire L F; Westcott S L; Jackson S P; Smerdon S J; Yaffe M B
CORPORATE SOURCE: Wellcome Trust/Cancer Research Campaign Institute of Cancer

and Developmental Biology and Department of Zoology
University of Cambridge CB2 1QR, Cambridge, United Kingdom.
CONTRACT NUMBER: GM60594 (NIGMS)
HL03601 (NHLBI)
SOURCE: MOLECULAR CELL, (2000 Nov) 6 (5) 1169-82.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1G6G
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020125
Entered Medline: 20020122

AB Forkhead-associated (FHA) domains are a class of ubiquitous signaling modules that appear to function through interactions with phosphorylated target molecules. We have used oriented peptide library screening to determine the optimal phosphopeptide binding motifs recognized by several FHA domains, including those within a number of DNA damage checkpoint kinases, and determined the **X-ray structure** of Rad53p-FHA1, in complex with a phospho-threonine peptide, at 1.6 A resolution. The structure reveals a striking similarity to the MH2 domains of Smad tumor suppressor proteins and reveals a mode of peptide binding that differs from SH2, 14-3-3, or PTB domain complexes. These results have important implications for DNA damage signaling and CHK2-dependent tumor suppression, and they indicate that FHA domains play important and unsuspected roles in S/T kinase signaling mechanisms in prokaryotes and eukaryotes.

L43 ANSWER 9 OF 53 MEDLINE
ACCESSION NUMBER: 2000108538 MEDLINE
DOCUMENT NUMBER: 20108538 PubMed ID: 10642179
TITLE: Protein-directed DNA structure II. Raman spectroscopy of a leucine zipper bZIP complex.
AUTHOR: Benevides J M; Li T; Lu X J; Srinivasan A R; Olson W K; Weiss M A; Thomas G J Jr
CORPORATE SOURCE: Division of Cell Biology and Biophysics, School of Biological Sciences, University of Missouri-Kansas City, Kansas City, MO 64110, USA.
CONTRACT NUMBER: GM20861 (NIGMS)
GM54378 (NIGMS)
HD33462 (NICHD)
SOURCE: BIOCHEMISTRY, (2000 Jan 25) 39 (3) 548-56.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000309
Last Updated on STN: 20030204
Entered Medline: 20000222

AB Mechanisms of transcription may involve protein-directed changes in DNA structure and DNA-directed changes in protein structure. We have employed Raman spectroscopy to characterize vibrational signatures associated with such induced molecular fitting for two classes of transcription factors-the basic leucine-zipper (bZIP) motif and the high-mobility-group (HMG) box-each with a DNA target site. Results for bZIP are described here; findings for the HMG-box are reported in the preceding paper in this issue [Benevides, J. M., Chan, G., Lu, X.-J., Olson, W. K., Weiss, M. A., and Thomas, G. J., Jr. (2000) Biochemistry 39, 537-547]. The yeast activator GCN4 provides a well-studied example of bZIP recognition, wherein B-DNA serves essentially as a template for protein folding. Analysis of Raman spectra of the 57-residue GCN4 bZIP domain, its AP-1 **binding site**, and their specific complex confirms a DNA-induced increase in alpha-helicity, attributable to folding of GCN4 basic arms with virtually no change in B-DNA structure, consistent with previous X-ray and **NMR structure** determinations. The absence of DNA perturbations in the bZIP model contrasts sharply with the HMG box, where DNA structure perturbations predominate. The bZIP and

HMG-box models represent two opposing extremes in a range of induced fits identifiable by Raman spectroscopy. Previously characterized lambda repressor/operator complexes [Benevides, J. M., Weiss, M. A., and Thomas, G. J. (1994) J. Biol. Chem. 269, 10869-10878] occupy an intermediate position within this range. A comprehensive tabulation of Raman markers proposed as diagnostic of different protein/DNA recognition motifs is presented. The results are analyzed in terms of available DNA crystal structures (Nucleic Acid Database) to identify details of DNA conformation that correlate with specific Raman recognition markers.

L43 ANSWER 10 OF 53 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999066591 EMBASE
TITLE: Kinetics of Cdc42 membrane extraction by Rho-GDI monitored by real-time fluorescence resonance energy transfer.
AUTHOR: Nomanbhoy T.K.; Erickson J.W.; Cerione R.A.
CORPORATE SOURCE: R.A. Cerione, Dept. of Molecular Medicine, VMC, Cornell University, Ithaca, NY 14853, United States
SOURCE: Biochemistry, (1999) 38/6 (1744-1750).
Refs: 21
ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The mechanisms underlying the ability of the Rho-GDP dissociation inhibitor (RhoGDI) to elicit the release of Rho-related GTP-binding proteins from membranes is currently unknown. In this report, we have set out to address this issue by using fluorescence resonance energy transfer approaches tO examine the functional interactions of the RhoGDI with membrane-associated Cdc42. Two fluorescence assays were developed to monitor the interactions between these proteins in real time. The first involved measurements of resonance energy transfer between N-methylanthraniloyl GDP (MantGDP) bound to Cdc42 and fluorescein maleimide covalently attached to cysteine 79 of RhoGDI (RhoGDI-FM). This assay allowed us to directly monitor the binding of RhoGDI to membrane-associated Cdc42. The second fluorescence assay involved measurements of resonance energy transfer between membrane-associated Cdc42 - MantGDP and hexadecyl(amino) fluorescein that was randomly inserted into the membrane bilayer. This assay enabled us to directly monitor the (GDI-induced) release of Cdc42 from membranes. Analyses of the rates of change in the fluorescence of Cdc42-MantGDP, which serves as a resonance energy transfer donor in both of these assays, as a function of RhoGDI concentration suggests a two-step mechanism to explain the ability of RhoGDI to stimulate the release of Cdc42 from membranes. Specifically, we propose that the GDI first binds rapidly to membrane-associated Cdc42 and then a slower isomerization occurs which represents the rate-limiting step for the dissociation of the Cdc42 - RhoGDI complex from membranes. We propose that this slow step in the observed kinetics reflects the time-course of translocation of the geranyl- geranyl lipid tail of Cdc42 from the outer leaflet of the membrane to the isoprenyl **binding site** observed in the previously reported **NMR structure** of the Cdc42 - RhoGDI complex [Gosser et al. (1997) Nature 387, 814].

L43 ANSWER 11 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1999:282874 SCISEARCH
THE GENUINE ARTICLE: 184EE
TITLE: The use of dipolar couplings for determining the solution structure of rat apo-S100B(beta beta)
AUTHOR: Drohat A C; Tjandra N; Baldisseri D M; Weber D J (Reprint)
CORPORATE SOURCE: UNIV MARYLAND, SCH MED, DEPT BIOCHEM & MOL BIOL, 108 N GREENE ST, BALTIMORE, MD 21201 (Reprint); UNIV MARYLAND, SCH MED, DEPT BIOCHEM & MOL BIOL, BALTIMORE, MD 21201; NHLBI, BIOPHYS CHEM LAB, NIH, BETHESDA, MD 20892
COUNTRY OF AUTHOR: USA
SOURCE: PROTEIN SCIENCE, (APR 1999) Vol. 8, No. 4, pp. 800-809.
Publisher: CAMBRIDGE UNIV PRESS, 40 WEST 20TH STREET, NEW YORK, NY 10011-4211.
ISSN: 0961-8368.
DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 54

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The relative orientations of adjacent structural elements without many well-defined NOE contacts between them are typically poorly defined in **NMR structures**. For apo-S100B(PP) and the structurally homologous protein calcyclin, the solution structures determined by conventional NMR exhibited considerable differences and made it impossible to draw unambiguous conclusions regarding the Ca2+-induced conformational change required for target protein binding. The structure of rat apo-S100B(PP) was recalculated using a large number of constraints derived from dipolar couplings that were measured in a dilute liquid crystalline phase. The dipolar couplings orient bond vectors relative to a single-axis system, and thereby remove much of the uncertainty in NOE-based structures. The structure of apo-S100B(PP) indicates a minimal change in the first, pseudo-EF-hand Ca2+ **binding site**, but a large reorientation of helix 3 in the second, classical EF-hand upon Ca2+ binding.

L43 ANSWER 12 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1999:438135 SCISEARCH
THE GENUINE ARTICLE: 202VD
TITLE: Crystal structure of a phosphatidylinositol 3-phosphate-specific membrane-targeting motif, the FYVE domain of Vps27p
AUTHOR: Misra S; Hurley J H (Reprint)
CORPORATE SOURCE: NIDDKD, MOL BIOL LAB, NIH, BETHESDA, MD 20892 (Reprint); NIDDKD, MOL BIOL LAB, NIH, BETHESDA, MD 20892
COUNTRY OF AUTHOR: USA
SOURCE: CELL, (28 MAY 1999) Vol. 97, No. 5, pp. 657-666. Publisher: CELL PRESS, 1050 MASSACHUSETTES AVE, CIRCULATION DEPT, CAMBRIDGE, MA 02138. ISSN: 0092-8674.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 64

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Phosphatidylinositol 3-phosphate regulates membrane trafficking and signaling pathways by interacting with the FYVE domains of target proteins. The 1.15 Angstrom structure of the Vps27p FYVE domain reveals two antiparallel beta sheets and an alpha helix stabilized by two Zn2+-binding clusters. The core secondary structures are similar to a rabphilin-3A Zn2+-binding domain and to the C1 and LIM domains. Phosphatidylinositol 3-phosphate binds to a pocket formed by the (R/K)(R/K)HHCR motif. A lattice contact shows how anionic ligands can interact with the phosphatidylinositol 3-phosphate-**binding site**. The tip of the FYVE domain has basic and hydrophobic surfaces positioned so that nonspecific interactions with the phospholipid bilayer can abet specific binding to phosphatidylinositol 3-phosphate.

L43 ANSWER 13 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1999:490206 SCISEARCH
THE GENUINE ARTICLE: 208AB
TITLE: Structural analysis of the lymphocyte-specific kinase Lck in complex with non-selective and Src family selective kinase inhibitors
AUTHOR: Zhu X T (Reprint); Kim J L; Newcomb J R; Rose P E; Stover D R; Toledo L M; Zhao H L; Morgenstern K A
CORPORATE SOURCE: KINETIX PHARMACEUT INC, MEDFORD, MA 02155 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: STRUCTURE WITH FOLDING & DESIGN, (15 JUN 1999) Vol. 7, No. 6, pp. 651-661. Publisher: CURRENT BIOLOGY LTD, 34-42 CLEVELAND STREET, LONDON W1P 6LE, ENGLAND. ISSN: 0969-2126.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 63

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: The lymphocyte-specific kinase Lck is a member of the Src family of non-receptor tyrosine kinases. Lck catalyzes the initial phosphorylation of T-cell receptor components that is necessary for signal transduction and T-cell activation. On the basis of both biochemical and genetic studies, Lck is considered an attractive cell-specific target for the design of novel T-cell immunosuppressants. To date, the lack of detailed structural information on the mode of inhibitor binding to Lck has limited the discovery of novel Lck inhibitors.

Results: We report here the high-resolution crystal structures of an activated Lck kinase domain in complex with three structurally distinct ATP-competitive inhibitors: AMP-PNP (a non-selective, non-hydrolyzable ATP analog); staurosporine (a potent but non-selective **protein kinase** inhibitor); and PP2 (a potent Src family selective protein tyrosine kinase inhibitor). Comparison of these structures reveals subtle but important structural changes at the ATP-**binding site** . Furthermore, PP2 is found to access a deep, hydrophobic pocket near the ATP-binding cleft of the enzyme; this binding pocket is not occupied by either AMP-PNP or staurosporine.

Conclusions: The potency of staurosporine against Lck derives in part from an induced movement of the glycine-rich loop of the enzyme upon binding of this ligand, which maximizes the van der Waals interactions present in the complex. In contrast, PP2 binds tightly and selectively to Lck and other Src family kinases by making additional contacts in a deep, hydrophobic pocket adjacent to the ATP-**binding site**; the amino acid composition of this pocket is unique to Src family kinases. The structures of these Lck complexes offer useful structural insights as they demonstrate that kinase selectivity can be achieved with small-molecule inhibitors that exploit subtle topological differences among **protein kinases**.

L43 ANSWER 14 OF 53 MEDLINE

ACCESSION NUMBER: 1999293073 MEDLINE
DOCUMENT NUMBER: 99293073 PubMed ID: 10362524
TITLE: A model of the complex between cyclin-dependent kinase 5 and the activation domain of neuronal Cdk5 activator.
AUTHOR: Chou K C; Watenpaugh K D; Heinrikson R L
CORPORATE SOURCE: Computer-Aided Drug Discovery, Pharmacia & Upjohn, Kalamazoo, Michigan 49007-4940, USA.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1999 Jun 7) 259 (2) 420-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990714
Last Updated on STN: 20020420
Entered Medline: 19990628

AB Tau **protein kinase** II (TPKII) is a heterodimer comprising a catalytic cyclin-dependent kinase subunit (Cdk5) and a regulatory protein called neuronal Cdk5 activator (Nck5a). TPKII is somewhat reminiscent, therefore, of the Cdk2-cyclin complex important in cell cycle regulation. In fact, although the amino acid sequence of Nck5a has little similarity to those of cyclins, recent experimental results obtained by site-directed mutagenesis studies have indicated that its activation domain, Nck5a*, may adopt a conformation of the cyclin-fold structure. Based on this structural inference, a 3-dimensional model of the Cdk5-Nck5a*-ATP complex was derived from the **X-ray structure** of Cdk2-cyclinA-ATP complex. The computed structure for TPKII is fully compatible with experimental data derived from studies of the Cdk5-Nck5a system, and also predicts which amino acid residues might be involved in formation of the Cdk5-Nck5a* interface and ATP binding pocket in TPKII. The computational structure also shows the interactive region of Nck5a* and the T-loop of Cdk5, a critical region in TPKII which functions as a gate-control-lever of the catalytic cleft. Furthermore, a physical mechanism is put forth to explain why the activation of TPKII is not dependent upon phosphorylation of the Cdk5 subunit, a puzzle long-standing in this area. These findings provide a model with which to consider design of compounds which might serve as inhibitors of TPKII.

Copyright 1999 Academic Press.

L43 ANSWER 15 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1998:634826 SCISEARCH
THE GENUINE ARTICLE: 110MZ
TITLE: cAMP response element-binding protein monomers cooperatively assemble to form dimers on DNA
AUTHOR: Wu X L; Spiro C; Owen W G; McMurray C T (Reprint)
CORPORATE SOURCE: MAYO CLIN & MAYO FDN, DEPT PHARMACOL, 200 1ST ST SW, ROCHESTER, MN 55905 (Reprint); MAYO CLIN & MAYO FDN, DEPT PHARMACOL, ROCHESTER, MN 55905; MAYO CLIN & MAYO FDN, DEPT BIOCHEM & MOL BIOL, ROCHESTER, MN 55905; GRAD SCH, ROCHESTER, MN 55905
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (14 AUG 1998) Vol. 273, No. 33, pp. 20820-20827.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 59
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have analyzed the properties of cAMP response element-binding protein (CREB) in solution with emphasis on dimerization and effects of phosphorylation. Using a purified CREB fusion protein, a novel dye-label technique, and sedimentation equilibrium analysis, we directly and conclusively demonstrate that, unlike Jun and Fos, CREB dimerization is DNA-dependent. CREB exists primarily as a monomer in solution and cooperatively assembles on DNA to form dimers. Sedimentation equilibrium analysis also indicates that dimerization is unaffected by cAMP-dependent **protein kinase**-phosphorylation or by the symmetry of the cAMP-responsive element **binding site**. Filter binding assays reveal that CREB binding is unaffected by phosphorylation regardless of the symmetry of the cAMP-responsive element **binding site**. Our results suggest that structurally similar members of the same bZIP superfamily may differ significantly in their regulation at the level of dimerization.

L43 ANSWER 16 OF 53 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998357533 EMBASE
TITLE: Structure of the Ets-1 pointed domain and mitogen-activated **protein kinase** phosphorylation site.
AUTHOR: Slupsky C.M.; Gentile L.N.; Donaldson L.W.; Mackereth C.D.; Seidel J.J.; Graves B.J.; McIntosh L.P.
CORPORATE SOURCE: L.P. McIntosh, Department of Biochemistry, 2146 Health Sciences Mall, University of British Columbia, Vancouver, BC V6T 1Z3, Canada. mcintosh@otter.biochem.ubc.ca
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (13 Oct 1998) 95/21 (12129-12134).
Refs: 37
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The Pointed (PNT) domain and an adjacent mitogen-activated protein (MAP) kinase phosphorylation site are defined by sequence conservation among a subset of ets transcription factors and are implicated in two regulatory strategies, protein interactions and posttranslational modifications, respectively. By using **NMR**, we have determined the **structure** of a 110- residue fragment of murine Ets-1 that includes the PNT domain and MAP kinase site. The Ets-1 PNT domain forms a monomeric five-helix bundle. The architecture is distinct from that of any known DNA- or protein-binding module, including the helix-loop-helix fold proposed for the PNT domain of the ets protein TEL. The MAP kinase site is in a highly flexible region of both the unphosphorylated and phosphorylated forms of the Ets-1 fragment. Phosphorylation alters neither

the structure nor monomeric state of the PNT domain. These results suggest that the Ets-1 PNT domain functions in heterotypic protein interactions and support the possibility that target recognition is coupled to structuring of the MAP kinase site.

L43 ANSWER 17 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1998:725540 SCISEARCH
THE GENUINE ARTICLE: 120JV
TITLE: Molecular basis for **protein kinase** C isozyme-selective binding: The synthesis, folding, and phorbol ester binding of the cysteine-rich domains of all **protein kinase** C isozymes
AUTHOR: Irie K (Reprint); Oie K; Nakahara A; Yanai Y; Ohigashi H; Wender P A; Fukuda H; Konishi H; Kikkawa U
CORPORATE SOURCE: KYOTO UNIV, GRAD SCH AGR, DIV APPL LIFE SCI, KYOTO 6068502, JAPAN (Reprint); STANFORD UNIV, DEPT CHEM, STANFORD, CA 94305; NIHON PERSEPT LTD, MINATO KU, TOKYO 1060032, JAPAN; KOBE UNIV, BIOSIGNAL RES CTR, KOBE, HYOGO 6578501, JAPAN
COUNTRY OF AUTHOR: JAPAN; USA
SOURCE: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (16 SEP 1998) Vol. 120, No. 36, pp. 9159-9167.
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
ISSN: 0002-7863.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS; LIFE
LANGUAGE: English
REFERENCE COUNT: 64
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **protein kinase** C (PKC) family of enzymes plays a crucial role in cellular signal transduction and tumor promotion. Conventional and novel PKC isozymes consist of a catalytic domain for protein phosphorylation and a regulatory domain which binds the endogenous messenger diacyl glycerol or exogenous agents such as phorbol esters. The N-terminal regulatory region of these isozymes contains two cysteine-rich domains (C1A and C1B, also known as CRD1 and CRD2), both of which are candidates for the phorbol ester-**binding site**. To determine the phorbol ester-**binding sites** of these isozymes and to elucidate the structural requirements for isozyme selective PKC modulation, the C1 peptides, consisting of ca. 50 amino acids of all conventional and novel PKCs, along with those of atypical PKCs have been synthesized by a solid-phase Fmoc strategy. Exceptionally high overall yields (10-20%) were achieved in the syntheses of most of the C1 peptides on a Pioneer Peptide Synthesizer (PerSeptive Biosystems) through the use of HATU as a coupling reagent. These peptides were successfully folded by zinc treatment, as monitored by CD spectroscopy. Importantly, only the C1Bs of all conventional and novel PKCs, except for PKC gamma, bound [H-3]phorbol-12,13-dibutyrate (PDBu) with high affinities, comparable to those of the native isozymes. Of special significance, both C1 peptides of PKC gamma, (i.e., gamma-C1A and gamma-C1B) exhibited high-affinity binding, providing the structural basis for a novel approach to PKC gamma-selective modulators, compounds of potential significance for the treatment of neuropathic pain. The effects of metal cations other than zinc on the binding of these isozymes were also investigated. Only the PKC gamma surrogates (gamma-C1A and gamma-C1B), when treated with cadmium, exhibited no binding, while other similarly treated conventional and novel PKC surrogates strongly bound PDBu, as did the zinc-folded peptides. These results suggest that cadmium ion could serve as a new and effective tool for controlling the activation of PKC gamma.

L43 ANSWER 18 OF 53 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998283981 MEDLINE
DOCUMENT NUMBER: 98283981 PubMed ID: 9618462
TITLE: The design, computer modeling, solution structure, and biological evaluation of synthetic analogs of bryostatin 1.
AUTHOR: Wender P A; DeBrabander J; Harran P G; Jimenez J M; Koehler M F; Lippa B; Park C M; Siedenbiedel C; Pettit G R
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA 94305-5080, USA.. wender@saurus.stanford.edu

CONTRACT NUMBER: CA31845 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Jun 9) 95 (12) 6624-9. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 19980716
Entered Medline: 19980709

AB The bryostatins are a unique family of emerging cancer chemotherapeutic candidates isolated from marine bryozoa. Although the biochemical basis for their therapeutic activity is not known, these macrolactones exhibit high affinities for **protein kinase** C (PKC) isozymes, compete for the phorbol ester **binding site** on PKC, and stimulate kinase activity in vitro and in vivo. Unlike the phorbol esters, they are not first-stage tumor promoters. The design, computer modeling, **NMR** solution **structure**, PKC binding, and functional assays of a unique class of synthetic bryostatin analogs are described. These analogs (7b, 7c, and 8) retain the putative recognition domain of the bryostatins but are simplified through deletions and modifications in the C4-C14 spacer domain. Computer modeling of an analog prototype (7a) indicates that it exists preferentially in two distinct conformational classes, one in close agreement with the crystal structure of bryostatin 1. The solution structure of synthetic analog 7c was determined by NMR spectroscopy and found to be very similar to the previously reported structures of bryostatins 1 and 10. Analogs 7b, 7c, and 8 bound strongly to PKC isozymes with Ki = 297, 3.4, and 8.3 nM, respectively. Control 7d, like the corresponding bryostatin derivative, exhibited weak PKC affinity, as did the derivative, 9, lacking the spacer domain. Like bryostatin, acetal 7c exhibited significant levels of in vitro growth inhibitory activity (1.8-170 ng/ml) against several human cancer cell lines, providing an important step toward the development of simplified, synthetically accessible analogs of the bryostatins.

L43 ANSWER 19 OF 53 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998241352 MEDLINE
DOCUMENT NUMBER: 98241352 PubMed ID: 9572845
TITLE: Binding of the **protein kinase** PKR to RNAs with secondary structure defects: role of the tandem A-G mismatch and noncontiguous helixes.
AUTHOR: Bevilacqua P C; George C X; Samuel C E; Cech T R
CORPORATE SOURCE: Department of Chemistry and Biochemistry, Howard Hughes Medical Institute, University of Colorado, Boulder, Colorado 80309-0215, USA.
SOURCE: BIOCHEMISTRY, (1998 May 5) 37 (18) 6303-16. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980618
Last Updated on STN: 19980618
Entered Medline: 19980608

AB The human interferon-induced double-stranded RNA (dsRNA)-activated **protein kinase** (PKR) is an antiviral agent that is activated by long stretches of dsRNA. PKR can also be activated or repressed by a series of cellular and viral RNAs containing non-Watson-Crick motifs. PKR has a dsRNA-binding domain (dsRBD) that contains two tandem copies of the dsRNA-binding motif (dsRBM). In vitro selection experiments were carried out to search for RNAs capable of binding to a truncated version of PKR containing the dsRBD. RNA ligands were selected by binding to His6-tagged proteins and chromatography on nickel(II) nitrilotriacetic acid agarose. A series of RNAs was selected that bind either similar to or tighter than a model dsRNA stem loop. Examination of these RNAs by a variety of methods, including sequence comparison, free-energy minimization, structure mapping, boundary experiments, site-directed mutagenesis, and footprinting, revealed

protein-**binding sites** composed of noncontiguous helices. In addition, selected RNAs contained tandem A-G mismatches (5'AG3'/3'GA5'), yet bound to the truncated protein with affinities similar to duplexes containing only Watson-Crick base pairs. The **NMR structure** of the tandem A-G mismatch in an RNA helix (rGGCAGGCC)2 reveals a global A-form helix with minor perturbations at the mismatch [Wu, M., SantaLucia, J., Jr., and Turner, D. H. (1997) Biochemistry 36, 4449-4460]. This supports the notion that dsRBM-containing proteins can bind to RNAs with secondary structure defects as long as the RNA has an overall A-form geometry. In addition, selected RNAs are able to activate or repress wild-type PKR autophosphorylation as well as its phosphorylation of protein synthesis initiation factor eIF-2, suggesting full-length PKR can bind to and be regulated by RNAs containing a tandem A-G mismatch.

L43 ANSWER 20 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1998:364391 SCISEARCH
THE GENUINE ARTICLE: ZL949
TITLE: Structural examination of the influence of phosphorylation on the binding of fibrinopeptide A to bovine thrombin
AUTHOR: Maurer M C; Peng J L; An S S; Trosset J Y; HenschenEdman A; Scheraga H A (Reprint)
CORPORATE SOURCE: CORNELL UNIV, BAKER LAB CHEM, ITHACA, NY 14853 (Reprint); CORNELL UNIV, BAKER LAB CHEM, ITHACA, NY 14853; CORNELL UNIV, BIOTECHNOL RESOURCE CTR, ITHACA, NY 14853; UNIV CALIF IRVINE, DEPT MOL BIOL & BIOCHEM, IRVINE, CA 92697
COUNTRY OF AUTHOR: USA
SOURCE: BIOCHEMISTRY, (28 APR 1998) Vol. 37, No. 17, pp. 5888-5902

Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
ISSN: 0006-2960.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 85

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Upon addition of thrombin, fibrinopeptides A and B are cleaved off from the N-termini of four chains of fibrinogen (A alpha B beta gamma)(2), and sites of polymerization are exposed, resulting in formation of a fibrin clot. For the fibrinogen A alpha chain, cleavage occurs most prevalently at the Arg16-Gly17 peptide bond. About 25-30% of the human fibrinogen A alpha chains are phosphorylated in nature at the position of Ser3, but the function for this modification is not understood. Previous NMR studies indicated chat the N-terminal portion ((1)ADSGE(5)) of unphosphorylated fibrinopeptide A does not interact with the surface of bovine thrombin. Kinetic and NMR studies have now been carried out to assess whether phosphorylation at Ser3 allows the N-terminal segment ((1)ADSGEGDFLAEGGGVR(16)) to become anchored on the thrombin surface, leading to formation of a catalytically more efficient enzyme-substrate complex. Kinetic results indicate that phosphorylation leads to an approximately 65% increase in substrate specificity (k(cat)/K-m) toward hydrolysis of fibrinogen A alpha(1-20). P-31 NMR studies reveal that the phosphorylated group does interact with thrombin, and H-1 line broadening studies suggest that phosphorylation does promote binding of amino acids 1-5. Two-dimensional transferred nuclear Overhauser effect spectroscopy studies of bound fibrinopeptide A(1-16 Ser3P) indicate that phosphorylation allows new through-space interactions involving amino acid residues (1)ADSGE(5) to be observed. Computational docking of the peptide onto the **X-ray structure** of thrombin suggests that the phosphate may interact with basic residues at the rim of the heparin **binding site** of thrombin. As a result, the phosphate may serve as an anionic linker between the fibrinopeptide and the enzyme thrombin.

L43 ANSWER 21 OF 53 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:657322 CAPLUS
DOCUMENT NUMBER: 130:11946
TITLE: Structure of the double-stranded RNA-binding domain of the **protein kinase** PKR reveals the molecular basis of its dsRNA-mediated activation

AUTHOR(S): Nanduri, Sambasivarao; Carpick, Bruce W.; Yang, Yanwu; Williams, Bryan R. G.; Qin, Jun
CORPORATE SOURCE: Structural Biology Program, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, 44195, USA
SOURCE: EMBO Journal (1998), 17(18), 5458-5465
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Protein kinase** PKR is an interferon-induced enzyme that plays a key role in the control of viral infections and cellular homeostasis. Compared with other known kinases, PKR is activated by a distinct mechanism that involves double-stranded RNA (dsRNA) binding in its N-terminal region in an RNA sequence-independent fashion. Here, the authors report the **NMR** soln. **structure** of the 20-kDa dsRNA-binding domain (dsRBD) of human PKR, which provides the 1st 3-dimensional insight into the mechanism of its dsRNA-mediated activation. The structure of dsRBD exhibited a dumb-bell shape comprising 2 tandem linked dsRNA-binding motifs (dsRBMs) both with an .alpha.-.beta.-.beta.-.beta.-.alpha. fold. The structure, combined with previous mutational and biochem. data, revealed a highly conserved RNA-**binding site** on each dsRBM and suggested a novel mode of protein-RNA recognition. The central linker was highly flexible, which may enable the 2 dsRBMs to wrap around the RNA duplex for cooperative and high-affinity binding, leading to an overall change in PKR conformation and in its activation.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L43 ANSWER 22 OF 53 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 6
ACCESSION NUMBER: 1998:471772 CAPLUS
DOCUMENT NUMBER: 129:254459
TITLE: Modulating multidrug resistance through inhibiting of **protein kinase** C activity by phenothiazines
AUTHOR(S): Liang, Wei; Yang, Chunzheng; Qi, Jing; Peng, Hui; Duan, Jianrong; Liu, Hanzhi; Zheng, Dexian
CORPORATE SOURCE: State Key Laboratory Experimental Hematology, Chinese Academy of Medical Sciences, Tianjin, 300020, Peop. Rep. China
SOURCE: Chinese Science Bulletin (1998), 43(14), 1196-1200
CODEN: CSBUEF; ISSN: 1001-6538
PUBLISHER: Science in China Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study, actions of phenothiazines (PTZ) in reversing multidrug resistance (MDR) and inhibiting **protein kinase** C (PKC) activity were investigated. It was found that the three PTZs caused 2.49, 36.58 and 75.78 fold reversal of K562/AO2 MDR cells resistant to adriamycin, resp., while the chemosensitizer verapamil caused 40 fold reversal in the same condition, indicating that PTZ11 is a novel reversal agent of MDR and a potential chemotherapeutic reagent for tumor therapy. PKC activity anal. in the presence of PTZs showed that PTZ6 and PTZ11 inhibited rat brain **protein kinase** C activity in a manner of dose-dependent. The IC50 values were (489.77) and (113) .mu.mol/L, resp. PTZ7 had no inhibition on PKC activity. Further study showed that PTZ11 could reduce PMA-mediated activation of PKC in a manner of dose-dependent, suggesting that PTZ11 might compete for the high-affinity phorbol ester **binding site** within PKC mol. Recently, an **x-ray structure** of PMA in complex with PKC Cys2 activator-binding domain was solved. The authors therefore decided to explore the possible binding model of PTZ11 with PKC mol. using SYBYL 6.02 program. It was shown that the **binding site** of PRTZ11 with PKC mol. partially overlapped with that of PMA, providing for the first time new data for designing PKC inhibitors and MDR reversal drugs.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L43 ANSWER 23 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI

ACCESSION NUMBER: 1998:665959 SCISEARCH
THE GENUINE ARTICLE: 114FN
TITLE: Crystal structure of JNK3: a kinase implicated in neuronal apoptosis
AUTHOR: Xie X L (Reprint); Gu Y; Fox T; Coll J T; Fleming M A; Markland W; Caron P R; Wilson K P; Su M S S
CORPORATE SOURCE: VERTEX PHARMACEUT INC, 130 WAVERLY ST, CAMBRIDGE, MA 02139 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: STRUCTURE, (15 AUG 1998) Vol. 6, No. 8, pp. 983-991. Publisher: CURRENT BIOLOGY LTD, 34-42 CLEVELAND STREET, LONDON W1P 6LB, ENGLAND. ISSN: 0969-2126.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: The c-Jun N-terminal kinases (JNKs) are members of the mitogen-activated protein (MAP) kinase family, and regulate signal transduction in response to environmental stress. Activation and nuclear localization of JNK3, a neuronal-specific isoform of JNK, has been associated with hypoxic and ischemic damage of CA1 neurons in the hippocampus. Knockout mice lacking JNK3 showed reduced apoptosis of hippocampal neurons and reduced seizure induced by kainic acid, a glutamate-receptor agonist. Thus, JNK3 may be important in the pathology of neurological disorders and is of significant medical interest.

Results: We report here the structure of unphosphorylated JNK3 in complex with adenylyl imidodiphosphate, an ATP analog. JNK3 has a typical kinase fold, with the ATP-**binding site** situated within a cleft between the N- and C-terminal domains. In contrast to other known MAP kinase structures, the ATP-**binding site** of JNK3 is well ordered; the glycine-rich nucleotide-binding sequence forms a beta-strand-turn-beta-strand structure over the nucleotide. Unphosphorylated JNK3 assumes an open conformation, in which the N- and C-terminal domains are twisted apart relative to their positions in cAMP-dependent **protein kinase**. The rotation leads to the misalignment of some of the catalytic residues. The phosphorylation lip of JNK3 partially blocks the substrate-**binding site**
.

Conclusions: This is the first JNK structure to be determined, providing a unique opportunity to compare structures from the three MAP kinase subfamilies. The structure reveals atomic-level details of the shape of JNK3 and the interactions between the kinase and the nucleotide. The misalignment of catalytic residues and occlusion of the active site by the phosphorylation lip may account for the low activity of unphosphorylated JNK3. The structure provides a framework for understanding the substrate specificity of different JNK isoforms, and should aid the design of selective JNK3 inhibitors.

L43 ANSWER 24 OF 53 MEDLINE
ACCESSION NUMBER: 1998394470 MEDLINE
DOCUMENT NUMBER: 98394470 PubMed ID: 9727487
TITLE: Crystal structure of a GCN5-related N-acetyltransferase: Serratia marcescens aminoglycoside 3-N-acetyltransferase.
AUTHOR: Wolf E; Vassilev A; Makino Y; Sali A; Nakatani Y; Burley S K
CORPORATE SOURCE: Laboratories of Molecular Biophysics, The Rockefeller University, New York, New York 10021, USA.
CONTRACT NUMBER: GM54762 (NIGMS)
SOURCE: CELL, (1998 Aug 21) 94 (4) 439-49. Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1BO4
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19981006
Last Updated on STN: 20030204
Entered Medline: 19980921

AB The **X-ray structure** of a canonical GCN5-related N-acetyltransferase (GNAT), Serratia marcescens aminoglycoside 3-N-acetyltransferase, bound to coenzyme A (CoA) has been determined at 2.3 A resolution. The single domain alpha/beta protein resembles a cupped right hand wrapped around a cylinder and consists of a highly curved, six-stranded beta sheet of mixed polarity that is sandwiched between four alpha helices. The structure includes all four conserved GNAT motifs (C, D, A, and B) and represents the catalytic core of this large enzyme superfamily. Acetyl CoA recognition is mediated by a betaalpha structure derived from GNAT motif A, which presents an invariant Arg/Gln-X-X-Gly-X-Gly/Ala segment for hydrogen bonding with the cofactor. Motif B contributes acidic residues to the **binding site** for the positively charged antibiotic substrate.

L43 ANSWER 25 OF 53 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:529706 CAPLUS
TITLE: The design, computer modeling, synthesis, solution structure, and biological evaluation of the first synthetic analogs of bryostatin.
AUTHOR(S): Wender, Paul A.; De Brabander, Jef; Harran, Patrick G.; Jimenez, Juan-Miguel; Koehler, Michael F. T.; Lippa, Blaise; Park, Cheol-Min
CORPORATE SOURCE: Department Chemistry, Stanford University, Stanford, CA, 94305, USA
SOURCE: Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), MEDI-221. American Chemical Society: Washington, D. C.
CODEN: 66KYA2
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The bryostatins are a unique family of emerging cancer chemotherapeutic candidates isolated from marine bryozoa. While the structural basis for their therapeutic activity is not known, these macrolactones exhibit high affinities for **protein kinase** C (PKC) isoenzymes and compete for the phorbol ester **binding site** on PKC. Unlike the phorbol esters, they do not induce tumor promotion. The design, computer modeling, synthesis, **NMR** soln. **structure**, PKC binding, and functional assays of the first members of a new class of synthetic bryostatin analogs will be described. The lead analogs bind with high affinity to PKC isoenzymes with Ki values in the low nanamolar region. These analogs also exhibited significant levels of in vitro growth inhibitory activity (1.8 - 170 ng / mL) against several human cancer cell lines, providing an important initial step toward the development of simplified, synthetically accessible analogs of the bryostatins. [Equation Omitted].

L43 ANSWER 26 OF 53 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97419134 MEDLINE
DOCUMENT NUMBER: 97419134 PubMed ID: 9271501
TITLE: **NMR structure** of a **protein kinase** C-gamma phorbol-binding domain and study of protein-lipid micelle interactions.
AUTHOR: Xu R X; Pawelczyk T; Xia T H; Brown S C
CORPORATE SOURCE: Glaxo-Wellcome Research and Development, Research Triangle Park, North Carolina 27709, USA.
SOURCE: BIOCHEMISTRY, (1997 Sep 2) 36 (35) 10709-17.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1TBN; PDB-1TBO
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970926
Last Updated on STN: 19970926
Entered Medline: 19970917
AB Classical **protein kinase** C (PKC) family members are activated by the binding of various ligands to one of several cysteine-rich domains of the enzyme. The natural agonist, diacylglycerol (DAG), and the natural product superagonist, phorbol dibutyrate (PDB), activate the enzyme to produce wide-ranging physiological effects. The

second cysteine-rich (Cys2) domain of rat brain PKC-gamma was expressed and labeled with 15N and 13C, and the solution structure was determined to high resolution using multidimensional heteronuclear NMR methods. The phorbol **binding site** was identified by titrating this domain with phorbol-12,13-dibutyrate (PDB) in the presence of organic cosolvents. Titrations of this domain with lipid micelles, in the absence and presence of phorbols, indicate selective broadening of some resonances. The observed behavior indicates conformational exchange between bound and free states upon protein-micelle interaction. The data also suggest that half of the domain, including the phorbol site and one of the zinc sites, is capable of inserting into membranes.

L43 ANSWER 27 OF 53 MEDLINE
ACCESSION NUMBER: 97238559 MEDLINE
DOCUMENT NUMBER: 97238559 PubMed ID: 9132009
TITLE: pKa measurements from nuclear magnetic resonance for the B1 and B2 immunoglobulin G-binding domains of protein G: comparison with calculated values for nuclear magnetic resonance and **X-ray structures**
.
AUTHOR: Khare D; Alexander P; Antosiewicz J; Bryan P; Gilson M; Orban J
CORPORATE SOURCE: Center for Advanced Research in Biotechnology, University of Maryland Biotechnology Institute, Rockville 20850, USA.
SOURCE: BIOCHEMISTRY, (1997 Mar 25) 36 (12) 3580-9.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970507
Last Updated on STN: 19970507
Entered Medline: 19970429

AB Two-dimensional homo- and heteronuclear nuclear magnetic resonance (NMR) spectroscopy was used to determine pKa values for all of the acidic residues in the B1 and B2 immunoglobulin G- (IgG-) binding domains of protein G. Due to the stability of protein G over a wide pH range, estimates of ionization constants were also obtained for some basic residues. These experimentally determined ionization constants were compared with values calculated from both X-ray and **NMR**-derived **structures** of B1 and B2 using the UHBD algorithm [Antosiewicz, J., et al. (1994) J. Mol. Biol. 238, 415-436]. This algorithm has been found to be predictive for pKa measurements in proteins and, in combination with experimental measurements, allowed some evaluation of the **NMR** and **X-ray structures**. Three regions where significant differences exist between the X-ray and **NMR structures** are (1) the position of the E56 side chain relative to the backbone amides of K10 and D40, (2) residues 33-37 in the helix, and (3) the Y45 side-chain conformation. For all three cases, the experimental pH titration curves are notably more consistent with the **X-ray structures** than the **NMR structures**. In contrast, a number of solvent-accessible side chains have experimental pKas more in agreement with mean pKas calculated from families of **NMR structures**. The conformations of these side chains may be susceptible to crystal packing effects. From titration experiments under basic conditions, it is noteworthy that the chemical shift of the Y45 C epsilonH resonance is invariant up to pDcorr 12. The Y45 side-chain hydroxyl group appears to maintain a nativelike hydrogen bond with D47 at pDcorr 12, even though the protein is approximately 90% unfolded. These results suggest that this short-range (i, i + 2) interaction, located in the beta3-beta4 hairpin, is present in the high-pH denatured state and may therefore form early in the folding of protein G.

L43 ANSWER 28 OF 53 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97244494 MEDLINE
DOCUMENT NUMBER: 97244494 PubMed ID: 9089334
TITLE: Structure-based design of a potent, selective, and irreversible inhibitor of the catalytic domain of the erbB receptor subfamily of protein tyrosine kinases.

AUTHOR: Singh J; Dobrusin E M; Fry D W; Haske T; Whitty A; McNamara D J
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48106-1047, USA. juswinder_singh@biogen. com.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1997 Mar 28) 40 (7) 1130-5.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970507
Last Updated on STN: 20000303
Entered Medline: 19970501

AB We report the use of structure-based drug design to create a selective erbB-1 (a.k.a. epidermal growth factor receptor) and erbB-2 (a.k.a. neu/her2 growth factor receptor) tyrosine kinase inhibitor. Using the X-ray crystal structure of the ternary complex of the cAMP-dependent Ser/Thr kinase together with a sequence alignment of the catalytic domains of a representative set of Ser/Thr and Tyr **protein kinases**, we have examined the nucleotide **binding site** for potential positions to attach an irreversible inhibitor. This information, combined with homology modeling of the erbB-1 and erbB-2 tyrosine kinase catalytic domains, has led to the identification of Cys797 of erbB1 and Cys805 of erbB2, which are structurally equivalent to Glu127 in the cAMP dependant Ser/Thr kinase as potential target residues. The **X-ray structure** of the cAMP Ser/Thr kinase shows Glu127 to be involved in a hydrogen-bonding interaction with the 2'-OH of the ribose portion of ATP. Using molecular modeling, it was predicted that the Cys side chains in erbB-1 and erbB-2 performed an analogous role, and it was postulated that the replacement of the 2'-OH of adenosine with a thiol might allow for a covalent bond to form. Since only erbB-1 and erbB-2 have a Cys at this position, the inhibitor should be selective. This model was subsequently tested experimentally by chemical synthesis of 2'-thioadenosine and assayed against the full length erbB-1 receptor and the catalytic domains of erbB-2, insulin receptor, beta-PDGF receptor, and the FGF receptor. Our results show that thioadenosine covalently inactivates erbB-1 with a second-order rate constant of k(max)/K(S) = 2000 +/- 500 M(-1) s(-1). Inactivation is fully reversed by 1 mM dithiothreitol, suggesting that inactivation involves the modification of a cysteine residue at the active site, presumably Cys797. The rate of inactivation saturates with increasing thioadenosine concentrations, suggesting that inactivation occurs through initial formation of a noncovalent complex with K(D) = 1.0 +/- 0.3 microM, followed by the slow formation of a disulfide bond with a rate constant of k(max) = (2.3 +/- 0.2) x 10(-3) s(-1). This approach may have application in the design of selective irreversible inhibitors against other members of the kinase family.

L43 ANSWER 29 OF 53 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:162826 CAPLUS
TITLE: PP1 and PP2A and the okadaic acid class of inhibitors.
AUTHOR(S): Gauss, Carla-Maria; Sheppeck, James E.; Chamberlin, A. Richard
CORPORATE SOURCE: Dept. Chemistry, U.C. Irvine, Irvine, CA, 92697, USA
SOURCE: Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), ORGN-564. American Chemical Society: Washington, D. C.
CODEN: 64AOAA
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB There is considerable interest in the elucidation of signaling pathways in the central nervous system, both between neurons, via neurotransmitters, and within them. The elements responsible for transmitting signals from membrane bound receptors to other destinations within the neuron comprise a complex system that is only partially understood. This project focuses on one aspect of that system, the reversible phosphorylation of Dopamine CAMP Regulated Phosphoprotein (DARPP) and its isoform Inhibitor-1 (I-1). These "mol. switches" are under the immediate control of **protein**

kinase A and protein phosphatases (PPs), the activities of which can in turn be modulated indirectly by extracellular events. There is a structurally diverse group of natural toxins which exert their cytotoxic effects by inhibiting PP2A and/or PP1, thereby preventing the dephosphorylation of DARPP and disrupting the normal signaling pathways. These toxins are collectively known as the Okadaic Acid class of inhibitors which includes okadaic acid, calyculin, microcystin LR, and tautomycin. They are competitive inhibitors; i.e., their PP1/PP2A **binding sites** overlap. A recently published **X -ray structure** of a PP1-microcystin LR complex provides a unique opportunity to explore binding interactions of all of these inhibitors with both PP1 and PP2A, and to develop new selective inhibitors based on these natural products.

L43 ANSWER 30 OF 53 MEDLINE
ACCESSION NUMBER: 97147285 MEDLINE
DOCUMENT NUMBER: 97147285 PubMed ID: 8994190
TITLE: Characterization of structural and functional properties of human 17 beta-hydroxysteroid dehydrogenase type 1 using recombinant enzymes and site-directed mutagenesis.
AUTHOR: Puranen T; Poutanen M; Ghosh D; Vihko P; Vihko R
CORPORATE SOURCE: Biocenter Oulu, University of Oulu, Finland.
CONTRACT NUMBER: DK-26546 (NIDDK)
SOURCE: MOLECULAR ENDOCRINOLOGY, (1997 Jan) 11 (1) 77-86.
Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970612
Last Updated on STN: 19970612
Entered Medline: 19970530

AB Human 17 beta-hydroxysteroid dehydrogenase (17-HSD) type 1 catalyzes the conversion of the low activity estrogen, estrone, into highly active estradiol, both in the gonads and in target tissues. The present study was carried out to characterize the dimerization, microheterogeneity, and phosphorylation of human 17-HSD type 1 and to evaluate the current model of hydride transfer and substrate recognition of the enzyme, based on its **x-ray structure**. 17-HSD type 1 is a homodimer consisting of noncovalently bound subunits, and the data in the present study indicate an exceptionally strong association between the monomers [dissociation constant (Kd) < 5 pmol/monomers liter]. Furthermore, substitutions constructed at the hydrophobic dimer interface always resulted in inactive aggregates of the protein. The enzyme was shown to be phosphorylated by **protein kinase** A exclusively at Ser134 only in vitro. However, in contrast to previous suggestions, phosphorylation of Ser134 was shown to play no role in the activity or microheterogeneity of human 17-HSD type 1. The presence of microheterogeneity in the recombinant enzyme also indicates that it does not result from the frequent protein polymorphism previously found for the enzyme. In line with the **x-ray structure** and the proposed catalytic mechanism of the enzyme, our results indicate that Ser142, Tyr155, and Lys159 are all critical for hydride transfer in human 17-HSD type 1. In contrast, the proposed interaction between His221, Glu282, and the 3-OH group of the steroid at the substrate recognition helix could not be shown to exist. Neither of these residues plays a critical role in the catalytic action of the enzyme in cultured cells.

L43 ANSWER 31 OF 53 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 9
ACCESSION NUMBER: 1996:262821 CAPLUS
DOCUMENT NUMBER: 124:283107
TITLE: The three-dimensional solution structure of the SH2 domain from p56blk kinase
AUTHOR(S): Metzler, William J.; Leiting, Barbara; Pryor, Kelly; Mueller, Luciano; Farmer, Bennett T., II
CORPORATE SOURCE: Departments of Macromolecular NMR, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA
SOURCE: Biochemistry (1996), 35(20), 6201-11

CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Signal transduction in B cells is mediated, in part, by the interaction of the cytoplasmic components of the antigen receptor complex and various members of the src family tyrosine kinases. Key to this process appears to be the interaction of the tyrosine kinase SH2 domains with the tyrosine-phosphorylated cytoplasmic domain of Ig-.alpha., a disulfide-bonded heterodimeric (with Ig-.beta. or Ig-.gamma.) transmembrane protein that noncovalently assocs. with the antigen receptor Ig chains. In addn. to binding to the phosphorylated cytoplasmic domains of Ig-.alpha. and Ig-.beta., blk and fyn(T), two members of the src family kinases, have been shown to bind overlapping but distinct sets of phosphoproteins. A comparison of their three-dimensional structures may elucidate the apparently subtle differences required for phosphoprotein discrimination. To begin characterizing the blk/fyn/phosphoprotein interactions, the authors have detd. the three-dimensional soln. structure of the SH2 domain of blk kinase by NMR spectroscopy. 1H, 13C, and 15N resonances of the SH2 domain of blk kinase were assigned by anal. of multidimensional, double- and triple-resonance NMR expts. Twenty structures of the blk SH2 domain were refined with the program X-PLOR using a total of 2080 exptl. derived conformational restraints. The structures converged to a root-mean-squared (rms) distance deviation of 0.51 and 0.95 .ANG. for the backbone atoms and for the non-hydrogen atoms, resp. The blk SH2 domain adopts the prototypical SH2 fold. Structurally, blk SH2 is most similar to the crystal structure of the v-src SH2 domain and superimposes on the crystal structure with an rmsd of 1.52 .ANG. for the backbone atoms. The largest deviations occur in the four loops interconnecting .beta.-strands A-E, which are the least well-defined regions in the **NMR structure**. Exclusion of these loops lowers this rmsd to 0.82 .ANG.. The conformation of the BC loop in the blk SH2 domain is similar to the open conformation in the apo lck SH2 domain, suggesting that, like the lck SH2 domain, the blk SH2 domain may have a gated phosphopeptide **binding site**. Finally, it is proposed that the amino acid substitution of Lys 88 (blk) for Glu [fyn(T)] is important for the obsd. differences in specificity between blk and fyn(T) SH2 domains.

L43 ANSWER 32 OF 53 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 96265154 MEDLINE
DOCUMENT NUMBER: 96265154 PubMed ID: 8691452
TITLE: Molecular modeling and site-directed mutagenesis studies of a phorbol ester-**binding site** in **protein kinase** C.
AUTHOR: Wang S; Kazanietz M G; Blumberg P M; Marquez V E; Milne G W
CORPORATE SOURCE: Laboratory of Medicinal Chemistry, Division of Basic Sciences, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1996 Jun 21) 39 (13) 2541-53.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960911
Last Updated on STN: 19960911
Entered Medline: 19960823

AB The **protein kinase** C (PKC) **binding site** used by PKC activators such as phorbol esters and diacylglycerols (DAGs) has been characterized by means of molecular modeling and site-directed mutagenesis studies. Based upon a **NMR** -determined solution **structure** of the second cysteinerich domain of PKC alpha, molecular modeling was used to study the structures of the complexes formed between the PKC receptor and a number of PKC ligands, phorbol esters, and DAGs. Site-directed mutagenesis studies identified a number of residues important to the binding of phorbol esters to PKC. Analysis of the molecular modeling and mutagenesis results allows the development of a binding model for PKC ligands for which the precise

binding nature is defined. The calculated hydrogen bond energies between the protein and various ligands in this binding model are consistent with their measured binding affinities. The **binding site** for phorbol esters and DAGs is located in a highly conserved, hydrophobic loop region formed by residues 6-12 and 20-27. For the binding elements in phorbol esters, the oxygen at C20 contributes most to the overall binding energy, and that at C3 plays a significant role. The oxygen atom at C12 is not directly involved in the interaction between phorbol esters and PKC. Our results also suggest that the oxygens at C9 and C13 are involved in PKC binding, while the oxygen at C4 is of minimal significance. These results are consistent with known structure-activity relationships in the phorbol ester family of compounds. Comparisons with the **X-ray structure** showed that although the X-ray data support the results for oxygens at C3, C12, and C20 of phorbol esters, they suggest different roles for oxygens at C4, C9, and C13. Several factors which may contribute to these discrepancies are discussed.

L43 ANSWER 33 OF 53 MEDLINE
ACCESSION NUMBER: 96174820 MEDLINE
DOCUMENT NUMBER: 96174820 PubMed ID: 8599943
TITLE: Mutant bZip-DNA complexes with four quasi-identical protein-DNA interfaces.
AUTHOR: Suc

binding nature is defined. The calculated hydrogen bond energies between the protein and various ligands in this binding model are consistent with their measured binding affinities. The **binding site** for phorbol esters and DAGs is located in a highly conserved, hydrophobic loop region formed by residues 6-12 and 20-27. For the binding elements in phorbol esters, the oxygen at C20 contributes most to the overall binding energy, and that at C3 plays a significant role. The oxygen atom at C12 is not directly involved in the interaction between phorbol esters and PKC. Our results also suggest that the oxygens at C9 and C13 are involved in PKC binding, while the oxygen at C4 is of minimal significance. These results are consistent with known structure-activity relationships in the phorbol ester family of compounds. Comparisons with the **X-ray structure** showed that although the X-ray data support the results for oxygens at C3, C12, and C20 of phorbol esters, they suggest different roles for oxygens at C4, C9, and C13. Several factors which may contribute to these discrepancies are discussed.

L43 ANSWER 33 OF 53 MEDLINE
ACCESSION NUMBER: 96174820 MEDLINE
DOCUMENT NUMBER: 96174820 PubMed ID: 8599943
TITLE: Mutant bZip-DNA complexes with four quasi-identical protein-DNA interfaces.
AUTHOR: Suckow M; Lopata M; Seydel A; Kisters-Woike B; von Wilcken-Bergmann B; Muller-Hill B
CORPORATE SOURCE: Institut fur Genetik der Universitat zu Koln, Germany.
SOURCE: EMBO JOURNAL, (1996 Feb 1) 15 (3) 598-606.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19960513
Last Updated on STN: 20030204
Entered Medline: 19960430

AB The complex between the yeast transcriptional activator GCN4 and the palindromic ATF/CREB site 5'- A4T3G2A1C0*G0'T1'C2'A3'T4'-3' shows dyad symmetry. The basic region of GCN4 contains a segment of 18 amino acids with a partially palindromic sequence: N-LKRARNTEA*ARRSRARKL-C. Symmetric residues are underlined. Apart from the ATF/CREB site, GCN4 also binds well to the symmetric variants with guanine in position 4 (5'-G4T3G2A1C0*G0'T1'C2'A3'C4'-3') or thymine in position 0 (5'-A4T3G2A1T0*A0'T1'C2'A3'T4'-3'). The half-sites of these sequences can be regarded as short pseudo-palindromes with central guanine 2/cytosine 2' base pairs. We investigated whether the geometry of the peptide of the basic region of GCN4 could be functionally related to the pseudo-palindromic character of some target half-sites. Since inspection of the **X-ray structures** of GCN4-DNA complexes reveals that several amino acid-DNA interactions are symmetric within the wild-type half-complexes, we introduced mutations into a GCN4 bZip peptide that improve the symmetry of the peptide. We found that most of the constructs retain specific DNA recognition. For one mutant, we conclude that it is not only capable of forming DNA complexes showing the well-known overall dyad symmetry, but that the protein-DNA interface of each half-complex can be divided further into two quasi-identical, quasi-symmetric substructures.

L43 ANSWER 34 OF 53 MEDLINE
ACCESSION NUMBER: 97162986 MEDLINE
DOCUMENT NUMBER: 97162986 PubMed ID: 9009833
TITLE: How Ras-related proteins talk to their effectors.
AUTHOR: Wittinghofer A; Nassar N
CORPORATE SOURCE: Max-Planck-Institut fur Molekulare Physiologie, Dortmund, Germany.. Alfred.Wittinghofer@mpi-dortmund.mpg.de
SOURCE: TRENDS IN BIOCHEMICAL SCIENCES, (1996 Dec) 21 (12) 488-91.
Ref: 36
Journal code: 7610674. ISSN: 0968-0004.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 20000303
Entered Medline: 19970227

AB More and more effectors for the Ras-related protein superfamily are being discovered and it is emerging that these GTP-binding proteins interact with more than one effector to generate more than one cellular signal. Atomic details for the interaction of Rap/Ras with one of the effectors, the **protein kinase** c-Raf-1, have recently become available by **X-ray structure** analysis. The implications for the specificity of the signal transduction pathway, and how the GTP-dependent switch mechanism modulates the interaction with effectors will be discussed here, using Ras as a paradigm.

L43 ANSWER 35 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 96:91408 SCISEARCH
THE GENUINE ARTICLE: TQ498
TITLE: STRUCTURE OF THE PSEUDOSUBSTRATE RECOGNITION SITE OF CHICKEN SMOOTH-MUSCLE MYOSIN LIGHT-CHAIN KINASE
AUTHOR: BARDEN J A (Reprint); SEHGAL P; KEMP B E
CORPORATE SOURCE: UNIV SYDNEY, DEPT ANAT & HISTOL, SYDNEY, NSW 2006, AUSTRALIA (Reprint); ST VINCENTS INST MED RES, MELBOURNE, NSW 3065, AUSTRALIA
COUNTRY OF AUTHOR: AUSTRALIA
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA-PROTEIN STRUCTURE AND MOLECULAR ENZYMOLOGY, (04 JAN 1996) Vol. 1292, No. 1, pp. 106-112.
ISSN: 0167-4838.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 37
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The structure of the chicken smooth muscle myosin light chain kinase pseudosubstrate sequence MLCK(774-807)amide was studied using two-dimensional proton NMR spectroscopy. Resonance assignments were made with the aid of totally correlated and nuclear Overhauser effect spectroscopy. A distance geometry algorithm was used to profess the body of NMR distance and angle data and the resulting family of structures was further refined using dynamic simulated annealing. The major structural features determined include two helical segments extending from Asp-777 to Lys-785 and from Arg-790/Met-791 to Trp-800 connected by a turn region from Leu-786 to Asp-789 enabling the helices to interact in solution. The C-terminal helix incorporates the bulk of the pseudosubstrate recognition site which is partially overlapped by the calmodulin **binding site** while the N-terminal helix forms the bulk of the connecting peptide. The demonstrated turn between the helices may assist in enabling the autoregulatory or pseudosubstrate recognition sequence to be rotated out of the active site of the catalytic core following calmodulin binding.

L43 ANSWER 36 OF 53 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:688426 CAPLUS
DOCUMENT NUMBER: 126:16202
TITLE: Determination of the solution structure of the SH3 domain of human p56 Lck tyrosine kinase
AUTHOR(S): Hiroaki, Hidekazu; Klaus, Werner; Senn, Hans
CORPORATE SOURCE: Pharmaceutical Research, F. Hoffman-La Roche AG, Basel, CH-4070, Switz.
SOURCE: Journal of Biomolecular NMR (1996), 8(2), 105-122
CODEN: JBNME9; ISSN: 0925-2738
PUBLISHER: ESCOM
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The soln. structure of the SH3 domain of human p56 Lck tyrosine kinase (Lck-SH3) was detd. by multidimensional heteronuclear NMR spectroscopy. The structure was calcd. from a total of 935 exptl. restraints comprising 785 distance restraints derived from 1017 assigned NOE cross-peaks and 150 dihedral angle restraints derived from 160 vicinal coupling consts. A novel combination of the const.-time 1H-13C NMR correlation expt. recorded

with various delays of the const.-time refocusing delays and a fractionally 13C-labeled sample was exploited for the stereospecific assignment of prochiral Me groups. Addnl., 28 restraints of 14 identified H-bonds were included. A family of 25 conformers was selected to characterize the soln. structure. The av. root-mean-square deviations of the backbone atoms (N, C.alpha., C', O) among the 25 conformers was 0.42 .ANG. for residues 7-63. The N- and C-terminal residues, 1-6 and 64-81, were disordered, whereas the well-converged residues 7-63 corresponded to the conserved sequences of other SH3 domains. The topol. of the SH3 structure comprised 5 antiparallel .beta.-strands arranged to form 2 perpendicular .beta.-sheets, which were concave and twisted in the middle part. The overall secondary structure and the backbone conformation of the core .beta.-strands were almost identical to the previously published **x-ray structure** of the fragment contg. the SH2-SH3 domains of p56 Lck. The **x-ray structure** of the SH3 domain in the tandem SH2-SH3 fragment was spatially included within the ensemble of the 25 NMR conformers, except for the segment of residues 14-18, which made intermol. contacts with an adjacent SH2 mol. and the phosphopeptide ligand in the crystal lattice. Local structural differences from other known SH3 domains were also obsd., the most prominent of which was the absence in Lck-SH3 of the 2 addnl. short .beta.-strands in the regions Ser-15 to Glu-17 and Gly-25 to Glu-27 flanking the so-called RT-Src loop. This loop (residues Glu-17 to Leu-24), together with the n-Src loop (residues Gln-37 to Ser-46) confined the ligand interaction site which was formed by a shallow patch of hydrophobic amino acids (His-14, Tyr-16, Trp-41, Phe-54, and Phe-59). Both loops were flexible and belonged to the most mobile regions of the protein, which was assessed by the heteronuclear 15N,1H-NOE values characterizing the degree of internal backbone motions. The arom. residues of the ligand **binding site** were arranged such that they formed 3 pockets for interactions with the polyproline ligand.

L43 ANSWER 37 OF 53 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 97027957 MEDLINE
DOCUMENT NUMBER: 97027957 PubMed ID: 8874044
TITLE: Rational design of a new C-myristylamido peptide exerting potent and selective PKC inhibitory activity.
AUTHOR: Zaliani A; Gromo G; Pinori M; Mascagni P
CORPORATE SOURCE: Italfarmaco Research Centre, Milan, Italy.
SOURCE: DRUG DESIGN AND DISCOVERY, (1996 Apr) 13 (3-4) 63-74.
Journal code: 9200627. ISSN: 1055-9612.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970203

AB A 3D model of the catalytic domain of PKC was built based on the **X-ray structure** of the homologous PKA enzyme. The two enzymes were found to have similar general architecture although differing for the number of negatively charged clusters and their location near the phosphorylation site. These differences were consistent with the charge requirements deduced from the consensus sequence of PKC and PKA substrates. A Myristyl **Binding Site** (MBS) was found in the PKC model between helix C and sheets 8 and 9. The identification of this MBS allowed the rationalization of the results obtained with N-myristoylated peptide inhibitors and, above all, the design of ITF1671 (H-RFARKGALRQKN-CONH-Myr), a new C-myristylamido peptide, which exerted one of the most potent inhibitory activity against PKC and PKM known to-date.

L43 ANSWER 38 OF 53 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 95394953 MEDLINE
DOCUMENT NUMBER: 95394953 PubMed ID: 7665608
TITLE: Residues in the second cysteine-rich region of **protein kinase** C delta relevant to phorbol ester binding as revealed by site-directed mutagenesis.
AUTHOR: Kazanietz M G; Wang S; Milne G W; Lewin N E; Liu H L;

Blumberg P M
CORPORATE SOURCE: Molecular Mechanisms of Tumor Promotion Section, NCI, National Institutes of Health, Bethesda, Maryland 20892-4255, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Sep 15) 270 (37) 21852-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951020
Last Updated on STN: 20000303
Entered Medline: 19951012

AB Phorbol esters bind with high affinity to **protein kinase** C (PKC) isozymes as well as to two novel receptors, n-chimaerin and Unc-13. The cysteine-rich regions present in these proteins were identified as the **binding sites** for the phorbol ester tumor promoters and the lipophilic second messenger sn-diacylglycerol. A 50-amino-acid peptide comprising the second cysteine-rich region of PKC delta, expressed in Escherichia coli as a glutathione S-transferase (GST)-fusion protein, bound [3H]phorbol 12,13-dibutyrate (PDBu) with high affinity (Kd = 0.8 nM). Using the cDNA of that cysteine-rich region as a template, a series of 37 point mutations was generated by site-directed mutagenesis, and the mutated proteins were analyzed quantitatively for binding of [3H]PDBu and, as appropriate, for binding of the ultrapotent analog [3H]bryostatin 1. Mutants displayed one of three patterns of behavior: phorbol ester binding was completely abolished, binding affinity was reduced, or binding was not significantly modified. As expected, five of the six cysteines as well as the two histidines involved in Zn2+ coordination are critical for the interaction of the protein with the phorbol esters. In addition, mutations in several positions, including phenylalanine 3, tyrosine 8, proline 11, leucines 20, 21 and 24, tryptophan 21, glutamine 27, and valine 38 drastically reduced the interaction with the ligands. The effect of these mutations can be rationalized from the three-dimensional (**NMR**) **structure** of the cysteine-rich region. In particular, the C-terminal portion of the protein does not appear to be essential, and the loop comprising amino acids 20 to 28 is implicated in the binding activity.

L43 ANSWER 39 OF 53 MEDLINE
ACCESSION NUMBER: 96071179 MEDLINE
DOCUMENT NUMBER: 96071179 PubMed ID: 7479080
TITLE: A comparison of the different DNA binding specificities of the bZip proteins C/EBP and GCN4.
AUTHOR: Koldin B; Suckow M; Seydel A; von Wilcken-Bergmann B; Muller-Hill B
CORPORATE SOURCE: Institut fur Genetik, Universitat zu Koln, Germany.
SOURCE: NUCLEIC ACIDS RESEARCH, (1995 Oct 25) 23 (20) 4162-9.
Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 20030204
Entered Medline: 19951221

AB The bZip proteins GCN4 and C/EBP differ in their DNA binding specificities: GCN4 binds well to the pseudopalindromic AP1 site 5'-A4T3G2A1C0T1C2'A3'T4'-3' and to the palindromic ATF/CREB sequence 5'-A4T3G2A1-C0*G0'T1'C2'A3'T4'-3'; C/EBP preferentially recognizes the palindromic sequence 5'-A4T3T2G1C0*G0'C1'A2'-A3'T4'-3'. According to the **X-ray structures** of GCN4-DNA complexes, five residues of the basic region of GCN4 are involved in specific base contacts: asparagine -18, alanine -15, alanine -14, serine -11 and arginine -10 (numbered relative to the start point of the leucine zipper, which we define as +1). In the basic region of C/EBP position -14 is occupied by valine instead of alanine, the other four residues being identical. Here we analyse the role of valine -14 in C/EBP-DNA complex

formation. Starting from a C/EBP-GCN4 chimeric bZip peptide which displays C/EBP specificity, we systematically mutated position -14 of its basic region and characterized the DNA binding specificities of the 20 possible different peptides by gel mobility shift assays with various target sites. We present evidence that valine -14 of C/EBP interacts more strongly with thymine 2 than with cytosine 1' of the C/EBP **binding site**, unlike the corresponding alanine -14 of GCN4, which exclusively contacts thymine 1' of the GCN4 **binding sites**.

L43 ANSWER 40 OF 53 MEDLINE
ACCESSION NUMBER: 96102288 MEDLINE
DOCUMENT NUMBER: 96102288 PubMed ID: 7500340
TITLE: Crystal structure of a bZIP/DNA complex at 2.2 A: determinants of DNA specific recognition.
AUTHOR: Keller W; Konig P; Richmond T J
CORPORATE SOURCE: Institut fur Molekularbiologie und Biophysik, ETH-Honggerberg, Zurich, Switzerland.
SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (1995 Dec 8) 254 (4) 657-67. Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960217
Last Updated on STN: 20030204
Entered Medline: 19960118

AB The **X-ray structure** of the GCN4-bZIP protein bound to DNA containing the ATF/CREB recognition sequence has been refined at 2.2 A. The water-mediated interactions between the basic domain and DNA are revealed, and combined with a more accurate description of the direct contacts, further clarify how binding specificity is achieved. Water molecules extend the interactions of both invariant basic domain residues, asparagine 235 and arginine 243, beyond their direct base contacts. The slight bending of the basic domain alpha-helix around the DNA facilitates the linking of arginine 241, 243 and 245 to main-chain carbonyl oxygen atoms via water molecules, apparently stabilizing interactions with the DNA.

L43 ANSWER 41 OF 53 MEDLINE
ACCESSION NUMBER: 95124717 MEDLINE
DOCUMENT NUMBER: 95124717 PubMed ID: 7529917
TITLE: Catalytic activity and transformation potential of v-Src require arginine 385 in the substrate binding pocket.
AUTHOR: Senften M; Schenker G; Sowadski J M; Ballmer-Hofer K
CORPORATE SOURCE: Friedrich Miescher-Institute, Basel, Switzerland.
SOURCE: ONCOGENE, (1995 Jan 5) 10 (1) 199-203. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950223
Last Updated on STN: 20000303
Entered Medline: 19950214

AB Tyrosine kinase are important mediators of signal transduction in eukaryotic cells. In order to better understand the mechanism of catalysis we studied a set of mutants of the prototype tyrosine kinase, the c-Src protein, a homologue of the Rous Sarcoma virus oncogene. Based on an **X-ray structure** of cAMP-dependent **protein kinase** (cAPK) we mutated an arginine residue conserved in subdomain VI of all known kinases to a non-charged residue. This residue coordinates phosphate of the autophosphorylation site located in subdomain VII of cAPK and this interaction has been proposed to be crucial for substrate binding. The mutant R385A of c-Src had low kinase activity towards exogenous substrates yet was able to autophosphorylate at tyrosine 416. When introduced into an activated v-src gene the R385A mutation totally blocked cell transformation. Our data suggest that the function of the conserved arginine 385 is to coordinate the phosphate of

the autophosphorylation site and to provide in this way a stable template for substrate binding.

L43 ANSWER 42 OF 53 MEDLINE
ACCESSION NUMBER: 96048036 MEDLINE
DOCUMENT NUMBER: 96048036 PubMed ID: 7556139
TITLE: The catalytic subunit of cAMP-dependent **protein kinase** from Ascaris suum. The cloning and structure of a novel subtype of **protein kinase** A.
AUTHOR: Jung S; Hoffmann R; Rodriguez P H; Mutzel R; Hofer H W
CORPORATE SOURCE: Faculty of Biology, University of Konstanz, Germany.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1995 Aug 15) 232 (1) 111-7.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X69806
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951114

AB A complete cDNA clone encoding the catalytic subunit of cAMP-dependent **protein kinase** of Ascaris suum was constructed from two overlapping partial clones. The encoded sequence of 337 amino acids is 48% identical with the sequence of mouse C alpha subunit. Approximately the same low similarity was found with the sequence of the C subunit from another nematode, Caenorhabditis elegans. The N-terminal 14 amino acids and the myristoylation site of the mammalian protein are not contained in the enzyme from Ascaris. Two cysteines (Cys33 and Cys319) replace a basic residue in the N-terminal region and an acidic amino acid near the C-terminus which are conserved in all known C subunits from other sources. The substitutions provide the possibility of disulfide bridge formation between the N-terminal and C-terminal parts of the protein. There is strong evidence that a single gene encodes cAMP-dependent **protein kinase** in Ascaris. Modelling of the sequence into the coordinates of the **X-ray structure** of the mammalian enzyme suggest a high degree of conservation in the three-dimensional structure. However, structural variations occur at the surface of the protein near the catalytic cleft and are likely to account for the variations in substrate specificity previously observed between the purified **protein kinase** from Ascaris [Thalhofer, H. P., Daum, G., Harris, B. G. & Hofer, H. W. (1988) J. Biol. Chem. 263, 952-957] and the mammalian enzyme.

L43 ANSWER 43 OF 53 MEDLINE
ACCESSION NUMBER: 95061400 MEDLINE
DOCUMENT NUMBER: 95061400 PubMed ID: 7971270
TITLE: Replacement of invariant bZip residues within the basic region of the yeast transcriptional activator GCN4 can change its DNA binding specificity.
AUTHOR: Suckow M; Schwamborn K; Kisters-Woike B; von Wilcken-Bergmann B; Muller-Hill B
CORPORATE SOURCE: Institut fur Genetik der Universitat zu Koln, Germany.
SOURCE: NUCLEIC ACIDS RESEARCH, (1994 Oct 25) 22 (21) 4395-404.
Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 20030204
Entered Medline: 19941219

AB Two residues are invariant in all bZip basic regions: asparagine -18 and arginine -10 (we define the first leucine of the leucine zipper of GCN4 as +1). **X-ray structures** of two specific GCN4-DNA complexes (Ellenberger et al., Cell, 71, 1223-1237, 1992; Konig & Richmond, J. Mol. Biol., 233, 139-154, 1993) demonstrate the involvement of both residues in specific base pair recognition. We replaced either

asparagine -18 or arginine -10 with all other amino acids and tested the DNA binding properties of the resulting mutant peptides by gel mobility shift assays. Peptides with histidine -18 or tyrosine -10 bind with changed specificities to variants of the ATF/CREB site 5'A4T3G2A1C0*G0'T1'C2'A3'T4'3' with symmetric exchanges in positions 2/2' or 0/0', respectively. The double mutant with histidine -18 and tyrosine -10 combines the features of the parental single mutants and binds specifically to the respective double exchange target. Furthermore, the tyrosine -10 mutant clearly prefers the palindrome 5'ATGATATCAT3' over the corresponding pseudo-palindrome 5'ATGATTCA-T3', whereas the lysine -10 mutant binds better to the pseudo-palindromic AP1 site 5'ATGACTCAT3' than to the palindromic ATF/CREB site. Thus, although invariant within natural bZip proteins, asparagine -18 or arginine -10 can be functionally replaced by other amino acids, and their replacement can lead to new DNA binding specificities.

L43 ANSWER 44 OF 53 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 94222106 MEDLINE
DOCUMENT NUMBER: 94222106 PubMed ID: 8168546
TITLE: Stimulation of cGMP-dependent **protein kinase** I alpha by a peptide from its own sequence. An investigation by enzymology, circular dichroism and 1H **NMR** of the activity and **structure** of cGMP-dependent **protein kinase** I alpha-(546-576)-peptide amide.
AUTHOR: Huggins J P; Ganzhorn A J; Saudek V; Pelton J T; Atkinson R A
CORPORATE SOURCE: Marion Merrell Dow Research Institute, Strasbourg, France.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1994 Apr 1) 221 (1) 581-93.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940613
Last Updated on STN: 19970203
Entered Medline: 19940602

AB The structure of cGMP-dependent **protein kinase** I alpha-(546-576)-peptide amide (peptide-546) and its effects on cGMP-dependent **protein kinase** I alpha (G-kinase) have been studied. By primary sequence analysis and analogy to a peptide that stimulates **protein kinase** C, peptide-546 was predicted to form part of the protein/peptide **binding site** of G-kinase, and it was proposed that it would stimulate the enzyme by interaction with an autoinhibitory site. The portion of cAMP-dependent **protein kinase** analogous to peptide-546 forms part of the peptide substrate **binding site**, interacting with the peptide inhibitor residues Argp-2 and Phep-11 (where p is the pseudophosphorylation site), through residues at positions corresponding to Glu4, Pro10 and Ser13 in peptide-546. Peptide-546 is a reasonably potent G-kinase activator, increasing the turnover number with the peptide substrate Arg-Lys-Arg-Ser-Arg-Lys-Glu by about threefold with an activation constant that is about fivefold lower than the Km value of this peptide substrate. Peptide-546 does not appear to change the affinity of the enzyme for the above substrate, ATP or cGMP and does not affect the binding of [3H]cGMP to G-kinase. The activation does not seem to result from an interaction between peptide-546 and peptide substrates, and a kinetic scheme is proposed which is compatible with an action of peptide-546 on G-kinase independent of substrates. The activation is additive with that given by cGMP and causes the enzyme to enter a hitherto unrecognised superactive state. Peptide conformation has been monitored in mixed 2,2,2-trifluoroethanol/H2O solvents by circular dichroism: helical structure is observed in these mixtures when the 2,2,2-trifluoroethanol content is above 25%. The structure is lost only gradually on raising the temperature to 80 degrees C with no clear melting transition. Assignment of the resonances in the 1H-NMR spectrum has allowed the identification of elements of secondary structure from detected nuclear Overhauser effects. In particular, a helical segment from Met18 to Arg26 is observed. The four proline residues (Pro10, Pro11,

Pro15 and Pro17) are all seen to be in the trans conformation, although additional, weaker peaks in the spectra may correspond to a minor conformer in which one or more of the prolines is in a cis conformation. The N-terminal residues are less structured but show some helical character.(ABSTRACT TRUNCATED AT 400 WORDS)

L43 ANSWER 45 OF 53 MEDLINE
ACCESSION NUMBER: 95082022 MEDLINE
DOCUMENT NUMBER: 95082022 PubMed ID: 7990140
TITLE: Investigating the high affinity and low sequence specificity of calmodulin binding to its targets.
AUTHOR: Afshar M; Caves L S; Guimard L; Hubbard R E; Calas B; Grassy G; Haiech J
CORPORATE SOURCE: Centre de Biochimie Structurale CNRS UMR 9955, INSERM U414, University of Montpellier I, France.
CONTRACT NUMBER: GM 30861 (NIGMS)
SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (1994 Dec 16) 244 (5) 554-71. Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950124
Last Updated on STN: 19950124
Entered Medline: 19950112

AB Calmodulin (CaM) is a calcium binding protein that regulates a wide range of enzymes. Recently the structures of a number of complexes between CaM and synthetic target peptides have been determined. The peptides correspond to the CaM-binding domain of skeletal and smooth muscle myosin light-chain kinase (MLCK) and calmodulin-dependent **protein kinase** II alpha. Comparison of the peptide-free and peptide-bound structures reveals that CaM undergoes a large conformational change when forming a complex, resulting in the formation of a binding surface that provides for an optimal interaction with its target. In this work, the available co-ordinates of the **NMR** solution **structure** of CaM-skeletal MLCK peptide are used as a basis upon which several molecular models of binding are built. The detailed features of the protein's peptide binding surface are revealed through two-dimensional topographical projections. Negatively charged margins at the binding surface extremities interact strongly with basic peptide residues separated by nine or ten positions. The binding surface core is hydrophobic and displays a groove with four deep pockets, which can accommodate bulky peptide residues at relative positions 4 and 8 (pocket A), 11 (pocket B), 13 (pocket C), 14 and 17 (pocket D). Therefore, both electrostatic and van der Waals' features contribute to the high affinity binding. A search for alternative peptide placements in the binding tunnel reveals the dominant role of specific electrostatic interactions in the binding energy. Apolar interactions are more permissive, such that the hydrophobic side-chains that line the binding tunnel adapt in order to maintain favourable van der Waals' contacts. The model suggests that the structure can accommodate large peptide translations (up to 5 A) and a reversed peptide binding mode, with a little loss in binding interaction energy. These calculations are compared with available experimental data, providing a structural rationale for the low sequence specificity of the CaM target recognition.

L43 ANSWER 46 OF 53 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:201865 BIOSIS
DOCUMENT NUMBER: PREV199598216165
TITLE: Pleckstrin Homology (PH) Domains in Signal Transduction.
AUTHOR(S): Ingley, Evan; Hemmings, Brian A. (1)
CORPORATE SOURCE: (1) Friedrich Miescher Inst., Postfach 2543, CH-4002 Basel Switzerland
SOURCE: Journal of Cellular Biochemistry, (1994) Vol. 56, No. 4, pp. 436-443. ISSN: 0730-2312.
DOCUMENT TYPE: Article
LANGUAGE: English

AB A diverse array of molecules involved in signal transduction have recently been recognised as containing a new homology domain, the pleckstrin

homology (PH) domain. These include kinases (both serine/threonine and tyrosine specific), all currently known mammalian phospholipase Cs, GTPases, GTPase-activating proteins, GTPase-exchange factors, "adapter" proteins, cytoskeletal proteins, and kinase substrates. This has sparked a new surge of research into elucidating its structure and function. The **NMR** solution **structure** of the PH domains of beta-spectrin and pleckstrin (the N-terminal domain) both display a core consisting of seven anti-parallel beta-sheet strands. The carboxy terminus is folded into a long alpha-helix. The molecule is electrostatically polarised and contains a pocket which may be involved in the binding of a ligand. The PH domains overall topological relatedness to the retinoid binding protein family of molecules would suggest a lipid ligand could bind to this pocket. The prime function of the PH domain still remains to be elucidated. However, it has been shown to be important in signal transduction, most probably by mediating protein-protein interactions. An extended PH domain of the beta-adrenergic receptor kinase (beta-ARK), as well as that of several other molecules, can bind to beta-gamma subunits of the heterotrimeric G-proteins. The possibility that the PH domain, which is found in so many signalling molecules, being generally involved in beta-gamma binding is provocative of implicating these proteins in G-protein signal transduction. While the PH domain and the beta-gamma **binding site** appear to be concomitant in beta-ARK, detailed analysis indicates that the PH domain is not generally a beta-gamma binding domain. Thus, the race is on to find the ligands of each PH domain and determine a common nature to their interaction.

L43 ANSWER 47 OF 53 MEDLINE
ACCESSION NUMBER: 93275733 MEDLINE
DOCUMENT NUMBER: 93275733 PubMed ID: 8502548
TITLE: The DNA binding specificity of the basic region of the yeast transcriptional activator GCN4 can be changed by substitution of a single amino acid.
AUTHOR: Suckow M; von Wilcken-Bergmann B; Muller-Hill B
CORPORATE SOURCE: Institut fur Genetik, Universitat zu Koln, Germany.
SOURCE: NUCLEIC ACIDS RESEARCH, (1993 May 11) 21 (9) 2081-6. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930716
Last Updated on STN: 20030204
Entered Medline: 19930628

AB The **X-ray structure** of a GCN4 DNA complex (1) shows, that specific DNA binding of the GCN4 basic region is mediated by a complicated network of base pair and DNA backbone contacts. According to the **X-ray structure**, alanine -14 of the basic region of GCN4 (we define the first leucine of the leucine zipper as +1) makes a hydrophobic contact to the methyl group of the thymine next to the center of the GCN4 **binding site** 5' ATGACTCAT 3'. We tested the DNA binding properties of the nineteen derivatives of GCN4, which carry all possible amino acids in position -14 of the basic region. Substitution of alanine -14 of GCN4 by either asparagine or cysteine changes the DNA binding specificity. Serine in this position broadens the specificity for position 1 of the target, whereas other amino acids either retain or decrease GCN4 specificity.

L43 ANSWER 48 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 93:381020 SCISEARCH
THE GENUINE ARTICLE: LG332
TITLE: ISOLATION, IDENTIFICATION AND SYNTHESIS OF AN ENDOGENOUS ARACHIDONIC AMIDE THAT INHIBITS CALCIUM-CHANNEL ANTAGONIST 1,4-DIHYDROPYRIDINE BINDING
AUTHOR: JOHNSON D E; HEALD S L; DALLY R D; JANIS R A (Reprint)
CORPORATE SOURCE: MILES INC, MILES RES CTR, 400 MORGAN LANE, W HAVEN, CT, 06516
COUNTRY OF AUTHOR: USA
SOURCE: PROSTAGLANDINS LEUKOTRIENES AND ESSENTIAL FATTY ACIDS, (JUN 1993) Vol. 48, No. 6, pp. 429-437. ISSN: 0952-3278.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 23
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB This study was part of a broad search for endogenous regulators of L-type calcium channels. The screening for active fractions was done by measuring inhibition [H-3]1,4-dihydropyridine (DHP) binding to rat cardiac and cortex membranes. An inhibitory fraction, termed lyophilized brain hexane-extractable inhibitor (LBHI), was isolated from hexane extracts of lyophilized calf brain. The active substance was purified by a series of chromatographic steps. C-13 nuclear magnetic resonance (NMR), H-1 coherence spectroscopy (COSY) NMR and fast atom bombardment (FAB) mass spectroscopy suggested that LBHI was N-arachidonic acid-2-hydroxyethylamide. Synthesis of this substance and subsequent high performance liquid chromatography (HPLC) and **NMR** analysis confirmed this **structure**. Synthetic LBHI (SLBHI) inhibited [H-3]DHP binding to rat cortex membranes with an IC50 value of congruent-to 15 muM and a Hill coefficient of congruent-to 2. Saturation analysis in the presence of SLBHI showed a change in K(D) (equilibrium dissociation constant), but not maximal binding capacity (B(max)). SLBHI produced an increased dissociation rate, which, along with the Hill slope of > 1, suggested a non-competitive interaction with the DHP **binding site**. The results suggest that arachidonic acid derivatives may be endogenous modifiers of the DHP calcium antagonist **binding site**.

L43 ANSWER 49 OF 53 MEDLINE
ACCESSION NUMBER: 93389726 MEDLINE
DOCUMENT NUMBER: 93389726 PubMed ID: 8377181
TITLE: The **X-ray structure** of the GCN4-bZIP bound to ATF/CREB site DNA shows the complex depends on DNA flexibility.
AUTHOR: Konig P; Richmond T J
CORPORATE SOURCE: Institut fur Molekularbiologie und Biophysik ETH-Hongerberg, Zurich, Switzerland.
SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (1993 Sep 5) 233 (1) 139-54. Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931105
Last Updated on STN: 20030204
Entered Medline: 19931015

AB The **X-ray structure** of the DNA binding domain of the yeast transcriptional activator protein GCN4 bound to a DNA fragment containing the sequence of the perfectly symmetrical ATF/CREB site has been solved to 3.0 A resolution. The architecture of this specific recognition complex supports the current model for bZIP proteins: a homodimer of parallel alpha-helices form an interhelix coiled-coil region via the leucine zipper, and the two N-terminal basic regions fit into the major groove of half sites on opposite sides of the DNA double helix. The structure shows that DNA flexibility plays the predominant role in the preservation of protein contacts with the symmetric ATF/CREB site (ATGACGTCAT) as compared to the pseudo-symmetric AP-1 target site (ATGACTCAT), overcoming the positional displacement of functional groups introduced by the additional G.C base-pair at the center of the ATF/CREB sequence.

L43 ANSWER 50 OF 53 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 91293313 MEDLINE
DOCUMENT NUMBER: 91293313 PubMed ID: 1712319
TITLE: Characterization of a discontinuous epitope on annexin II by site-directed mutagenesis.
AUTHOR: Thiel C; Weber K; Gerke V
CORPORATE SOURCE: Max Planck Institute for Biophysical Chemistry, Gottingen, Germany.
SOURCE: FEBS LETTERS, (1991 Jul 8) 285 (1) 59-62. Journal code: 0155157. ISSN: 0014-5793.

PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910901
Last Updated on STN: 19960129
Entered Medline: 19910814

AB Recombinant annexin II mutants were generated to identify amino acids involved in the formation of the discontinuous epitope of the monoclonal antibody H28. Analysis of the various mutant proteins by immunoblotting and enzyme-linked immunosorbent assay revealed that residues Lys27, Arg62, Glu65, and Arg67 are indispensable for H28 reactivity. Residues in equivalent positions are also in close proximity in the recently determined **X-ray structure** of annexin V, a different member of the same family of Ca2+/lipid-binding proteins. Thus annexins II and V show a similar three-dimensional folding in this region of the molecule. Consequently, the Ca2+ **binding sites** and the residues phosphorylated by pp60src (Tyr23) and **protein kinase** C (Ser25) most likely reside on opposite sides of the annexin II molecule.

L43 ANSWER 51 OF 53 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 91:399386 SCISEARCH
THE GENUINE ARTICLE: FW003
TITLE: CHARACTERIZATION OF A DISCONTINUOUS EPITOPE ON ANNEXIN-II BY SITE-DIRECTED MUTAGENESIS
AUTHOR: THIEL C; WEBER K; GERKE V (Reprint)
CORPORATE SOURCE: MAX PLANCK INST BIOPHYS CHEM, POB 2841, W-3400 GOTTINGEN, GERMANY
COUNTRY OF AUTHOR: GERMANY
SOURCE: FEBS LETTERS, (1991) Vol. 285, No. 1, pp. 59-62.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 33
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Recombinant annexin II mutants were generated to identify amino acids involved in the formation of the discontinuous epitope of the monoclonal antibody H28. Analysis of the various mutant proteins by immunoblotting and enzyme-linked immunosorbent assay revealed that residues Lys27, Arg62, Glu65, and Arg67 are indispensable for H28 reactivity. Residues in equivalent positions are also in close proximity in the recently determined **X-ray structure** of annexin V, a different member of the same family of Ca2+/lipid-binding proteins. Thus annexins II and V show a similar three-dimensional folding in this region of the molecule. Consequently, the Ca2+ **binding sites** and the residues phosphorylated by pp60src (Tyr23) and **protein kinase** C (Ser25) most likely reside on opposite sides of the annexin II molecule.

L43 ANSWER 52 OF 53 MEDLINE
ACCESSION NUMBER: 87231944 MEDLINE
DOCUMENT NUMBER: 87231944 PubMed ID: 3035562
TITLE: Consensus topography in the ATP **binding site** of the simian virus 40 and polyomavirus large tumor antigens.
AUTHOR: Bradley M K; Smith T F; Lathrop R H; Livingston D M; Webster T A
CONTRACT NUMBER: CA38069 (NCI)
RR02275 (NCRR)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1987 Jun) 84 (12) 4026-30.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198707
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19970203

Entered Medline: 19870717

AB The location and sequence composition of a consensus element of the nucleotide **binding site** in both simian virus 40 (SV40) and polyomavirus (PyV) large tumor antigens (T antigens) can be predicted with the assistance of a computer-based pattern-matching system, ARIADNE. The latter was used to optimally align elements of T antigen primary sequence and predicted secondary structure with a "descriptor" for a mononucleotide binding fold. Additional consensus elements of the nucleotide **binding site** in these two proteins were derived from comparisons of T antigen primary and predicted secondary structures with **x-ray structures** of the nucleotide **binding sites** in four otherwise unrelated proteins. Each of these elements was predicted to be encompassed within a 110-residue segment that is highly conserved between the two T antigens residues 418-528 in SV40 T antigen and residues 565-675 in PyV). Results of biochemical and immunologic experiments on the nucleotide binding behavior of these proteins were found to be consistent with these predictions. Taken together, the latter have resulted in a topological model of the ATP **binding site** in these two oncogene products.

L43 ANSWER 53 OF 53 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1985:124946 BIOSIS
DOCUMENT NUMBER: BR29:14942
TITLE: THE ATP-**BINDING SITE** OF ADENYLATE KINASE HOMOLOGY TO F-1 ATPASE RAS-P-21 MYOSIN AND OTHER NUCLEOTIDE BINDING PROTEINS.
AUTHOR(S): FRY D C; KUBY S A; MILDVAN A S
CORPORATE SOURCE: JOHNS HOPKINS MED. SCH., BALTIMORE, MD.
SOURCE: 69TH ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, ANAHEIM, CALIF., USA, APR. 21-26, 1985. FED PROC, (1985) 44 (3), 672.
CODEN: FEPRA7. ISSN: 0014-9446.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

=> log y